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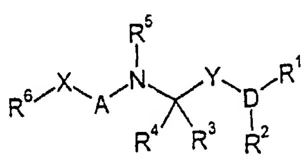
(54) Title: CYCLIC CARBOXYLIC ACIDS AS INTEGRIN ANTAGONISTS



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(57) Abstract: The present invention relates to compounds of general formula (I), processes for their preparation, pharmaceutical compositions containing them as well as their use for the production of pharmaceutical compositions for the treatment of inflammatory diseases.

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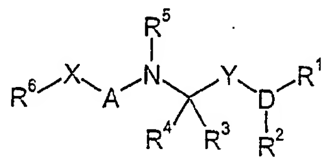
Cyclic carboxylic acids as integrin antagonists

The present invention relates to compounds of formula (I),



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their preparation and use as pharmaceutical compositions as integrin antagonists, especially as $\alpha_4\beta_1$ and/or $\alpha_4\beta_7$ and/or $\alpha_9\beta_1$ integrin antagonists and in particular for the production of pharmaceutical compositions suitable for the inhibition or the prevention of cell adhesion and cell-adhesion mediated disorders. Examples are the treatment and the prophylaxis of atherosclerosis, asthma, chronic obstructive pulmonary disease (COPD), allergies, diabetes, inflammatory bowel disease, multiple sclerosis, myocardial ischemia, rheumatoid arthritis, transplant rejection and other inflammatory, autoimmune and immune disorders.

Adhesive interactions between the leukocytes and endothelial cells play a critical role in leukocyte trafficking to sites of inflammation. These events are essential for normal host defense against pathogens and repair of tissue damage, but can also contribute to the pathology of a variety of inflammatory and autoimmune disorders. Indeed, eosinophil and T cell infiltration into the tissue is known as a cardinal feature of allergic inflammation such as asthma.

The interaction of circulating leukocytes with adhesion molecules on the luminal surface of blood vessels appears to modulate leukocyte transmigration. These vascular cell adhesion molecules arrest circulating leukocytes, thereby serving as the first step in their recruitment to infected or inflamed tissue sites. Subsequently, the leukocytes reaching the extravascular space interact with connective tissue cells such as fibroblasts as well as extracellular matrix proteins such as fibronectin, laminin, and collagen. Adhesion molecules on the leukocytes and on the vascular endothelium are

hence essential to leukocyte migration and attractive therapeutic targets for intervention in many inflammatory disorders.

Leukocyte recruitment to sites of inflammation occurs in a stepwise fashion beginning with leukocyte tethering to the endothelial cells lining the blood vessels. This is followed by leukocyte rolling, activation, firm adhesion, and transmigration. A number of cell adhesion molecules involved in those four recruitment steps have been identified and characterized to date. Among them, the interaction between vascular cell adhesion molecule 1 (VCAM-1) and very late antigen 4 (VLA-4, $\alpha_4\beta_1$ integrin), as well as the interaction between mucosal addressin cell adhesion molecule 1 (MAdCAM-1) and $\alpha_4\beta_7$ integrin, has been shown to mediate the tethering, rolling, and adhesion of lymphocytes and eosinophils, but not neutrophils, to endothelial cells under a physiologic flow condition. This suggests that the VCAM-1 / VLA-4 and/or MAdCAM-1 / $\alpha_4\beta_7$ integrin mediated interactions could predominantly mediate a selective recruitment of leukocyte subpopulations *in vivo*. The inhibition of this interaction is a point of departure for therapeutic intervention (A. J. Wardlaw, *J. Allergy Clin. Immunol.* **1999**, 104, 917-26).

VCAM-1 is a member of immunoglobulin (Ig) superfamily and is one of the key regulators of leukocyte trafficking to sites of inflammation. VCAM-1, along with intracellular adhesion molecule 1 (ICAM-1) and E-selectin, is expressed on inflamed endothelium activated by such cytokines as interleukin 1 (IL-1) and tumor necrosis factor α (TNF-α), as well as by lipopolysaccharide (LPS), via nuclear factor κB (NF-κB) dependent pathway. However, these molecules are not expressed on resting endothelium. Cell adhesion mediated by VCAM-1 may be involved in numerous physiological and pathological processes including myogenesis, hematopoiesis, inflammatory reactions, and the development of autoimmune disorders. Integrins VLA-4 and $\alpha_4\beta_7$ both function as leukocyte receptors for VCAM-1.

The integrin $\alpha_4\beta_1$ is a heterodimeric protein expressed in substantial levels on all circulating leukocytes except mature neutrophils. It regulates cell migration into tis-

sues during inflammatory responses and normal lymphocyte trafficking. VLA-4 binds to different primary sequence determinants, such as a QIDSP motif of VCAM-1 and an ILDVP sequence of the major cell type-specific adhesion site of the alternatively spliced type III connecting segment domain (CS-1) of fibronectin.

In vivo studies with neutralizing monoclonal antibodies and inhibitor peptides have demonstrated a critical role for α_4 integrins interaction in leukocyte-mediated inflammation. Blocking of VLA-4/ligand interactions, thus, holds promise for therapeutic intervention in a variety of inflammatory, autoimmune and immune diseases (Zimmerman, C.; *Exp. Opin. Ther. Patents* **1999**, *9*, 129-133).

Furthermore, compounds containing a bisarylurea moiety as a substituent were disclosed as $\alpha_4\beta_1$ integrin receptor antagonists: WO 96/22966, WO 97/03094, WO 99/33789, WO 99/37605. However, no aminobenzoic acids or aminocycloalkylcarboxylic acids or homologues thereof or heterocyclics analogues thereof with $\alpha_4\beta_1$ integrin receptor antagonists activity have been described.

3-[[[(phenylacetyl)amino]acetyl]amino]-benzoic acid has been described in Biochemistry, Vol. 26, No. 12, 1987, 3385 as a substrate for β–lactamases. N-(4-aminophenylacetylglycyl)-4-aminophenylacetic acid has been described in J. für prakt. Chem., 4. Reihe, Band 27, 1965, 63 without giving a pharmaceutical use. N^1-[4-(ethoxycarbonyl)phenyl]-N^2-(phenylacetyl)-α-glutamine and N^2-benzoyl-N^1-[4-(ethoxycarbonyl)phenyl]-α-glutamine and related compounds have been described in Minerva Medica, 58 (86), 1967, 3651 and NL 6510006 as antisecretory agents. (S)-4-[[4-carboxy-1-oxo-2-[(phenylacetyl)amino]butyl]amino]-benzeneacetic acid has been described in Drugs Exp. Clin. Res. Suppl. 1, XIII, 1987, 57 as antitumor agent. N-[2-[[4-aminosulfonyl)phenyl]amino]-2-oxoethyl]-N-ethylbenzeneacetamide has been described in Eur. J. Med. Chem.- Chim. Ther. 12 (4), 1977, 387 with schistosomicide activity. N-(2-phenylacetylamino-acetylamino)-benzoic acid ethyl ester has been described in Yakugaku Zasshi 79, 1959, 1606 in decomposition studies of penicil-

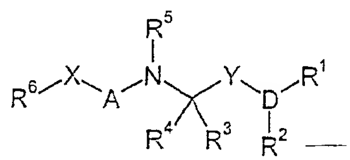
lins. Japanese publication Hei 11-269135 describes 3-aminosubstituted benzoic acid derivatives as selectin inhibitors.

None of these compounds have been described in relation to the inhibition or the prevention of cell adhesion and cell-adhesion mediated disorders.

Further to their $\alpha_4\beta_1$ integrin antagonistic activity, the compounds of the present invention may also be used as $\alpha_4\beta_7$ or $\alpha_9\beta_1$ integrin antagonists.

An object of the present invention is to provide new, alternative, aminobenzoic acids or aminocycloalkylcarboxylic acids or homologues thereof or heterocyclic analogues thereof derived integrin antagonists for the treatment of inflammatory, autoimmune and immune diseases.

The present invention therefore relates to compounds of the general formula (I):



(I)

wherein

R^1 represents a 4- to 9-membered saturated, unsaturated or aromatic cyclic residue,

which can contain 0 to 3 heteroatoms selected independently from the group N, S and O,

wherein the cyclic residue R^1 can be annulated with a 4- to 8-membered saturated, unsaturated or aromatic cyclic residue, which can contain 0 to 2 heteroatoms selected independently from the group N, S and O,

and wherein the cyclic residue R^1 and/or a ring annulated to the cyclic residue R^1 is substituted by 1 to 2 substituents $-R^{1-1}-R^{1-2}-R^{1-3}-Z$, wherein

R^{1-1} represents a bond, -O-, -S-, NR^{1-4}, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_6 or C_{10} aryl, C_3-C_7 cycloalkyl or a 4-9-membered saturated or unsaturated heterocyclic residue containing up to 3 heteroatoms selected from the group oxygen, nitrogen or sulfur,

wherein R^{1-1} can optionally be substituted by 1 to 2 substituents selected from the group R^{1-5},

wherein R^{1-5} represents hydrogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_6 or C_{10} aryl, C_3-C_7 cycloalkyl or a 4-9-membered saturated or unsaturated heterocyclic residue containing up to 3 heteroatoms selected from the group oxygen, nitrogen or sulfur,

wherein R^{1-5} can optionally be substituted by 1 to 3 substituents selected from the group C_1-C_4 alkyl, C_1-C_4 alkyloxy, phenyl, C_3-C_6 cycloalkyl, halogen, nitro, cyano, oxo,

R^{1-2} represents a bond, -O-, -S-, NR^{1-4}, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl,

wherein R^{1-2} can optionally be substituted by C_1-C_{10} alkyl, C_2-C_{10} alkenyl, $C_2 - C_{10}$ alkynyl or R^{1-6},

wherein R^{1-6} represents hydrogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_6 or C_{10} aryl, C_3-C_7 cycloalkyl or a 4-9-membered

saturated or unsaturated heterocyclic residue containing up to 3 heteroatoms selected from the group oxygen, nitrogen or sulfur,

wherein R^{1-6} can optionally be substituted by 1 to 3 substituents selected from the group C_1-C_4 alkyl, C_1-C_4 alkyloxy, phenyl, C_3-C_6 cycloalkyl, halogen, nitro, cyano, oxo,

R^{1-4} can optionally be hydrogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl or C_2-C_{10} alkynyl,

R^{1-3} represents a bond, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl,

wherein R^{1-3} can optionally be substituted by C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl or R^{1-7},

wherein R^{1-7} represents hydrogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_6 or C_{10} aryl, C_3-C_7 cycloalkyl or a 4-9-membered saturated or unsaturated heterocyclic residue containing up to 3 heteroatoms selected from the group oxygen, nitrogen or sulfur,

wherein R^{1-7} can optionally be substituted by 1 to 3 substituents selected from the group C_1-C_4 alkyl, C_1-C_4 alkyloxy, phenyl, C_3-C_6 cycloalkyl, halogen, nitro, cyano, oxo,

with the proviso that, where R^{1-3} is a bond, R^{1-2} is not a heteroatom,

and with the proviso that R^{1-1} and R^{1-2} are not both heteroatom at the same time,

Z represents $-C(O)OR^{Z-1}$, $-C(O)NR^{Z-2}R^{Z-3}$, $-SO_2NR^{Z-2}R^{Z-3}$, $-SO(OR^{Z-1})$, $-SO_2(OR^{Z-1})$, $-P(O)R^{Z-1}(OR^{Z-3})$, $-PO(OR^{Z-1})(OR^{Z-3})$ or 5-tetrazolyl,

wherein R^{Z-2} is hydrogen, C_1-C_4 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6 or C_{10} aryl, $-C(O)R^{Z-4}$ or $-SO_2R^{Z-4}$,

wherein R^{Z-4} is C_1-C_4 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6 or C_{10} aryl,

wherein R^{Z-4} can optionally be substituted by 1 to 3 substituents selected from the group halogen, nitro, cyano, oxo,

R^{Z-1} and R^{Z-3} are identical or different and represent hydrogen, C_1-C_4 alkyl, C_2-C_6 alkenyl, C_2 -C_6 alkynyl, C_3 -C_6 cycloalkyl, C_6 or C_{10} aryl or benzyl,

wherein R^{Z-1} and R^{Z-3} can optionally be substituted by 1 to 3 substituents selected from the group C_1-C_4 alkyl, C_1-C_4 alkyloxy, halogen, nitro, cyano,

the cyclic residue R^1 and/or a ring annulated to the cyclic residue formed by R^1 can optionally be substituted by 0 to 2 substituents R^{1-8}, halogen, nitro, amino, cyano and oxo,

wherein

R^{1-8} can independently be selected from the group of C_1-C_4 alkyl, C_1-C_4 alkyloxy, phenyl, phenoxy, phenylamino, C_3-C_6 cycloalkyl, and

R^2 represents hydrogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_6 or C_{10} aryl, C_3-C_7 cycloalkyl or a 4-9-membered saturated or unsaturated heterocyclic residue containing up to 2 heteroatoms selected from the group oxygen, nitrogen or sulfur,

which can optionally be substituted by 1 to 3 radicals R^{2-1},

wherein R^{2-1} represents C_{1-4} alkyl, trifluormethyl, trifluormethoxy, $-OR^{2-2}$, $-SR^{2-2}$, $NR^{2-3}R^{2-4}$, $-C(O)R^{2-2}$, $S(O)R^{2-2}$, $-SO_2R^{2-2}$, $-CO_2R^{2-2}$, $-OC(O)R^{2-2}$, $-C(O)NR^{2-3}R^{2-4}$, $-NR^{2-2}C(O)R^{2-3}$, $-SO_2NR^{2-3}R^{2-4}$, $NR^{2-2}SO_2R^{2-3}$, $-NR^{2-2}C(O)NR^{2-3}R^{2-4}$, $-NR^{2-2}C(O)OR^{2-3}$, $-OC(O)NR^{2-3}R^{2-4}$, halogen, cyano, nitro or oxo,

wherein R^{2-2} represents hydrogen, C_1-C_4 alkyl, $C_3 - C_6$ cycloalkyl, C_6 or C_{10} aryl

which can optionally be substituted by 1 substituent selected from the group C_1-C_4 alkyl, C_1-C_4 alkyloxy, phenyl, C_3-C_6 cycloalkyl, halogen, nitro, cyano,

and wherein R^{2-3} and R^{2-4} are identical or different and represent hydrogen, C_1-C_4 alkyl, C_2-C_6 cycloalkyl, C_6 or C_{10} aryl,

or

R^{2-3} and R^{2-4} together form a 4-7-membered ring, which includes the nitrogen atom to which R^{2-3} and R^{2-4} are bonded and which contains up to 2 additional heteroatoms selected from the group oxygen, nitrogen or sulfur and which contains up to 2 double bonds,

and if R^2 is alkyl, R^2 together with the cyclic residue R^1 and D can form a ring,

R^3 represents hydrogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_6 or C_{10} aryl, C_3-C_7 cycloalkyl or a 4-9-membered saturated or unsaturated heterocyclic residue containing up to 2 heteroatoms selected from the group oxygen, nitrogen or sulfur,

wherein R^3 can optionally be substituted by 1 to 3 radicals R^{3-1},

and wherein R^3 can furthermore be single-foldedly substituted by C_3-C_7 cycloalkyl, C_6 or C_{10} aryl, C_4-C_9 heteroaryl or a heterocyclic residue containing up to 2 heteroatoms selected from the group oxygen, nitrogen or sulfur, which can be annulated with a phenyl ring,

and which can optionally be substituted by 1 to 3 radicals R^{3-1},

wherein R^{3-1} represents C_1-C_4 alkyl, trifluormethyl, trifluormethoxy, $-OR^{3-2}$, $-SR^{3-2}$, $NR^{3-3}R^{3-4}$, $-C(O)R^{3-2}$, $S(O)R^{3-2}$, $-SO_2R^{3-2}$, $-OC(O)R^{3-2}$, $-C(O)NR^{3-3}R^{3-4}$, $-NR^{3-2}C(O)R^{3-3}$, $-SO_2NR^{3-3}R^{3-4}$, $NR^{3-2}SO_2R^{3-3}$, $-NR^{3-2}C(O)NR^{3-3}R^{3-4}$, $-NR^{3-2}C(O)OR^{3-3}$, $-OC(O)NR^{3-3}R^{3-4}$, $-CO_2R^{3-5}$, halogen, cyano, nitro or oxo,

wherein R^{3-2} represents hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_6 or C_{10} aryl

which can optionally be substituted by 1 substituent selected from the group C_1-C_4 alkyl, C_1-C_4 alkyloxy, phenyl, C_3-C_6 cycloalkyl, halogen, nitro, cyano,

and wherein R^{3-3} and R^{3-4} are identical or different and represent hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_6 or C_{10} aryl, benzyl or 9-fluorenylmethyl,

or

R^{3-3} and R^{3-4} together form a 4-7-membered ring, which includes the nitrogen atom to which R^{3-3} and R^{3-4} are bonded and which contains up to 2 additional heteroatoms selected from the group oxygen, nitrogen or sulfur and which contains up to 2 double bonds,

and wherein R^{3-5} represents C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_6 or C_{10} aryl

R^4 represents hydrogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_6 or C_{10} aryl, C_3-C_7 cycloalkyl or a 4-9-membered saturated or unsaturated heterocyclic residue containing up to 2 heteroatoms selected from the group oxygen, nitrogen or sulfur,

which can optionally be substituted by 1 to 3 radicals R^{4-1},

and which can furthermore be single-foldedly substituted by C_3-C_7 cycloalkyl, C_6 or C_{10} aryl, C_4-C_9 heteroaryl or a heterocyclic residue containing up to 2 heteroatoms selected from the group oxygen, nitrogen or sulfur,

which can optionally be substituted by 1 to 3 radicals R^{4-1},

wherein R^{4-1} represents $C_1 - C_4$ alkyl, trifluormethyl, trifluormethoxy, $-OR^{4-2}$, $-SR^{4-2}$, $NR^{4-3}R^{4-4}$, $-C(O)R^{4-2}$, $S(O)R^{4-2}$, $-SO_2R^{4-2}$, $-OC(O)R^{4-2}$, $-C(O)NR^{4-3}R^{4-4}$, $-NR^{4-2}C(O)R^{4-3}$, $-SO_2NR^{4-3}R^{4-4}$, $NR^{4-2}SO_2R^{4-3}$, $-NR^{4-2}C(O)NR^{4-3}R^{4-4}$, $-NR^{4-2}C(O)OR^{4-3}$, $-OC(O)NR^{4-3}R^{4-4}$, $-CO_2R^{4-5}$, halogen, cyano, nitro or oxo,

wherein R^{4-2} represents hydrogen, $C_1 - C_4$ alkyl, $C_3 - C_6$ cycloalkyl, C_6 or C_{10} aryl

which can optionally be substituted by 1 substituent selected from the group C_1-C_4 alkyl, C_1-C_4 alkyloxy, phenyl, C_3-C_6 cycloalkyl, halogen, nitro, cyano,

and wherein R^{4-3} and R^{4-4} are identical or different and represent hydrogen, C_{1-4} alkyl, C_3-C_6 cycloalkyl, C_6 or C_{10} aryl,

or

R^{4-3} and R^{4-4} together form a 4-7-membered ring, which includes the nitrogen atom to which R^{4-3} and R^{4-4} are bonded and which contains up to 2 additional heteroatoms selected from the group oxygen, nitrogen or sulfur and which contains up to 2 double bonds,

and wherein R^{4-5} represents $C_1 - C_4$ alkyl, $C_3 - C_6$ cycloalkyl, C_6 or C_{10} aryl

R^5 represents hydrogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_6 or C_{10} aryl, C_3-C_7 cycloalkyl or a 4-9-membered saturated or unsaturated heterocyclic residue containing up to 2 heteroatoms selected from the group oxygen, nitrogen or sulfur,

which can optionally be substituted by 1 to 3 radicals R^{5-1},

and which can furthermore be single-foldedly substituted by C_3-C_7 cycloalkyl, C_6 or C_{10} aryl, C_4-C_9 heteroaryl or a heterocyclic residue containing up to 2 heteroatoms selected from the group oxygen, nitrogen or sulfur,

which can optionally be substituted by 1 to 3 radicals R^{5-1},

wherein R^{5-1} represents C_1-C_4 alkyl, trifluormethyl, trifluormethoxy, $-OR^{5-2}$, $-SR^{5-2}$, $NR^{5-3}R^{5-4}$, $-C(O)R^{5-2}$, $S(O)R^{5-2}$, $-SO_2R^{5-2}$, $-CO_2R^{5-2}$, $-OC(O)R^{5-2}$, $-C(O)NR^{5-3}R^{5-4}$, $-NR^{5-2}C(O)R^{5-3}$, $-SO_2NR^{5-3}R^{5-4}$, $NR^{5-2}SO_2R^{5-3}$,

$-NR^{5-2}C(O)NR^{5-3}R^{5-4}$, $-NR^{5-2}C(O)OR^{5-3}$, $-OC(O)NR^{5-3}R^{5-4}$, halogen, cyano, nitro or oxo,

wherein R^{5-2} represents hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_6 or C_{10} aryl

which can optionally be substituted by 1 substituent selected from the group C_1-C_4 alkyl, C_1-C_4 alkyloxy, phenyl, C_3-C_6 cycloalkyl, halogen, nitro, cyano,

and wherein R^{5-3} and R^{5-4} are identical or different and represent hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_6 or C_{10} aryl,

or

R^{5-3} and R^{5-4} together form a 4-7-membered ring, which includes the nitrogen atom to which R^{5-3} and R^{5-4} are bonded and which contains up to 2 additional heteroatoms selected from the group oxygen, nitrogen or sulfur and which contains up to 2 double bonds,

R^6 represents phenyl or a 5- to 6-membered aromatic heterocyclic residue containing up to 3 heteroatoms independently selected from the group oxygen, nitrogen or sulfur,

which can optionally be annulated with a 5- to 8-membered saturated or unsaturated cyclic residue containing up to 2 heteroatoms independently selected from the group oxygen, nitrogen or sulfur,

and which can optionally be independently substituted by 1 to 3 radicals R^{6-1} and which can furthermore be single-foldedly substituted by C_3-C_7 cycloalkyl, C_6 or C_{10} aryl, C_4-C_9 heteroaryl or a heterocyclic residue containing up to 2 heteroatoms selected from the group oxygen, nitrogen or sulfur,

wherein the latter cyclic substituents can themselves optionally be substituted by 1 to 3 radicals R^{6-1},

wherein R^{6-1} represents C_1-C_4 alkyl, trifluormethyl, trifluormethoxy, $-OR^{6-4}$, $-SR^{6-2}$, $NR^{6-3}R^{6-4}$, $-C(O)R^{6-2}$, $S(O)R^{6-2}$, $-SO_2R^{6-2}$, $-CO_2R^{6-2}$, $-OC(O)R^{6-2}$, $-C(O)NR^{6-3}R^{6-4}$, $-NR^{6-2}C(O)R^{6-2}$, $-SO_2NR^{6-3}R^{6-4}$, $-NR^{6-2}SO_2R^{6-2}$, $-NR^{6-2}C(O)NR^{6-3}R^{6-4}$, $-NR^{6-2}C(O)OR^{6-4}$, $-OC(O)NR^{6-3}R^{6-4}$, halogen, cyano, nitro or oxo,

wherein R^{6-2} represents hydrogen, C_1-C_4 alkyl, C_3 – C_6 cycloalkyl, C_6 or C_{10} aryl

which can optionally be substituted by 1 to 3 substituents selected from the group C_1-C_4 alkyl, C_1-C_4 alkyloxy, phenyl, C_3-C_6 cycloalkyl, halogen, nitro, cyano,

and wherein R^{6-3} and R^{6-4} are identical or different and represent hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_6 or C_{10} aryl or a 4-9-membered saturated or unsaturated heterocyclic residue containing up to 2 heteroatoms selected from the group oxygen, nitrogen or sulfur,

which can optionally be substituted by 1 to 2 substituents selected from the group C_1-C_4 alkyl, phenyl, C_3-C_7 cycloalkyl, C_1-C_4 alkyloxy, halogen, nitro, cyano,

or

R^{6-3} and R^{6-4} together form a 4-7-membered ring, which includes the nitrogen atom to which R^{6-3} and R^{6-4} are bonded and which contains up to 2 additional heteroatoms selected from the group oxygen, nitrogen or

sulfur and which contains up to 2 double bonds, which can optionally be substituted by 1 to 2 substituents selected from the group C_1-C_4 alkyl, phenyl, benzyl, C_3-C_7 cycloalkyl, C_1-C_4 alkyloxy, halogen, nitro, cyano, oxo,

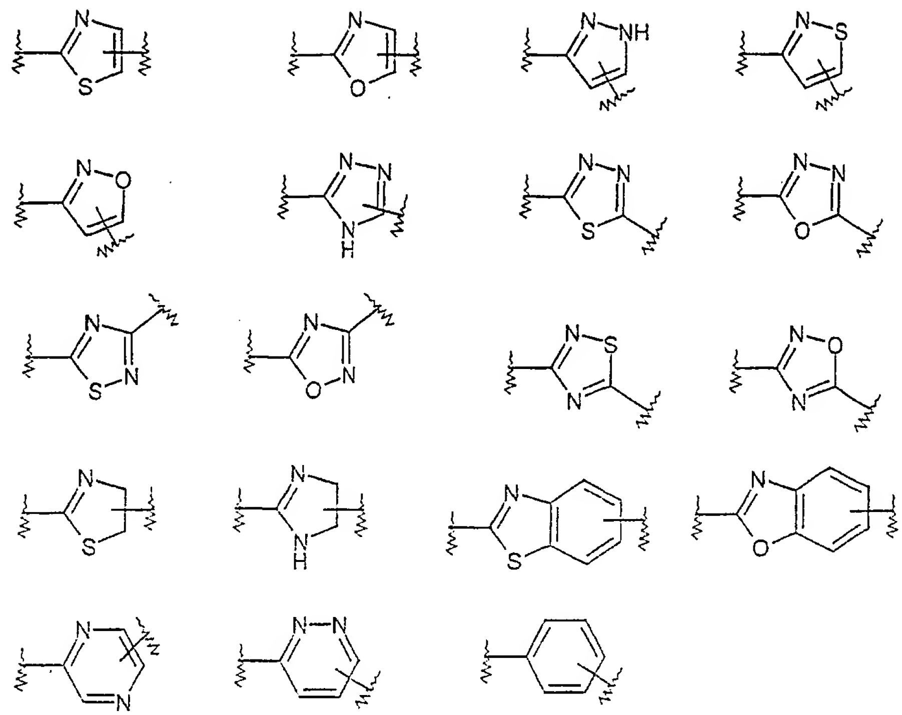
and in case that R^1 represents a 3-amino benzoic acid derivative and R^{6-1} represents $-OR^{6-4}$, $-C(O)NR^{6-3}R^{6-4}$ or $-NR^{6-2}C(O)R^{6-4}$, then R^{6-4} represents C_6 or C_{10} aryl or a 4-9-membered saturated or unsaturated heterocyclic residue containing up to 2 heteroatoms selected from the group oxygen, nitrogen or sulfur,

wherein the ring formed by R^{6-3} and R^{6-4} can optionally be substituted by 1 to 2 substituents selected from the group C_1-C_4 alkyl, phenyl, C_3-C_7 cycloalkyl, C_1-C_4 alkyloxy, halogen, nitro, cyano,

or

R^3 and R^4 or R^4 and R^5 together form a 4-7-membered saturated or unsaturated ring containing up to 2 heteroatoms selected from the group oxygen, nitrogen or sulfur, which can optionally be substituted by 1 to 2 substituents selected from the group C_1-C_4 alkyl, phenyl, benzyl, C_3-C_7 cycloalkyl, C_1-C_4 alkyloxy, halogen, nitro, cyano, oxo and which can be fused with a 3-7 membered homocyclic or heterocyclic, saturated, unsaturated or aromatic ring,

A represents -C(O)-, -C(O)-C(O)-, -SO-, $-SO_2-$, -PO-, $-PO_2-$, 2-pyrimidyl, 4-pyrimidyl, 2-pyridyl, 2-imidazolyl, 4-imidazolyl, 2-benzimidazolyl or a ring selected from the following group:



wherein the abovementioned ring systems can optionally be substituted by C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, nitro, amino, cyano,

X represents -$CR^{X-1}R^{X-2}$-,

wherein R^{X-1} and R^{X-2} can be independently selected from the group hydrogen, C_1-C_4 alkyl, C_2 - C_4 alkenyl, C_2-C_4 alkynyl,

or

together with R^6 form a 4-7-membered ring, which can contain up to 2 heteroatoms independently selected from the group oxygen, nitrogen or sulfur and containing up to 2 double bonds, which can optionally be substituted by 1 to 2 substituents selected from the group C_1-C_4 alkyl, phenyl, benzyl, C_3-C_7 cycloalkyl, C_1-C_4 alkyloxy, halogen, nitro, cyano, oxo,

Y represents bond, -C(O)-, -S(O)-, $-SO_2-$, -O-, -S-, $-CR^{Y-1}R^{Y-2}-$, or $-NR^{Y-3}$,

wherein R^{Y-1}, R^{Y-2}, R^{Y-3} can be independently selected from the group bond, hydrogen, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl,

and can optionally be substituted by 1 to 2 substituents independently selected from the group C_1-C_4 alkyl, phenyl, benzyl, C_3-C_7 cycloalkyl, C_1-C_4 alkyloxy, halogen, nitro, cyano, oxo,

D represents N or CR^{D-1},

wherein R^{D-1} can be independently selected from the group bond, hydrogen, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl,

and R^{D-1} can optionally be substituted by 1 to 2 substituents independently selected from the group C_1-C_4 alkyl, phenyl, benzyl, C_3-C_7 cycloalkyl, C_1-C_4 alkyloxy, halogen, nitro, cyano, oxo,

with the proviso that, where D represents –N-, Y does not represent –O- or -S-,

and the compound is not one of the following: 3-[[[(phenylacetyl)amino]acetyl]amino]-benzoic acid; N-(4-aminophenylacetylglycyl)-4-aminophenylacetic acid; N^1-[4-(ethoxycarbonyl)phenyl]-N^2-(phenylacetyl)-α-glutamine; N^2-benzoyl-N^1-[4-(ethoxycarbonyl)phenyl]-α-glutamine; (S)-4-[[4-carboxy-1-oxo-2-[(phenylacetyl)amino]butyl]amino]-benzeneacetic acid; N-[2-[[4-aminosulfonyl)phenyl]amino]-2-oxoethyl]-N-ethylbenzeneacetamide; N-(2-phenylacetylamino-acetylamino)-benzoic acid ethyl ester,

and pharmaceutically acceptable salts thereof.

In a preferred embodiment, the present invention relates to compounds of general formula (I),

wherein

R^1 represents a 4- to 6-membered saturated, unsaturated or aromatic cyclic residue,

which can contain 0 to 3 heteroatoms selected independently from the group N, S and O,

wherein the cyclic residue R^1 can be annulated with a 5- to 6-membered saturated, unsaturated or aromatic cyclic residue, which can contain 0 to 2 heteroatoms selected independently from the group N, S and O,

and wherein the cyclic residue R^1 and/or a ring annulated to the cyclic residue R^1 is substituted by 1 to 2 substituents $-R^{1-1}-R^{1-2}-R^{1-3}-Z$, wherein

R^{1-1} represents a bond, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or C_6 aryl,

wherein R^{1-1} can optionally be substituted by 1 substituent selected from the group R^{1-5}, wherein R^{1-5} represents hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl or C_6 aryl,

R^{1-2} represents a bond, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl

R^{1-3} represents a bond, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl

Z represents -C(O)OR^{Z-1}, -C(O)NR^{Z-2}R^{Z-3} or 5-tetrazolyl,

wherein R^{Z-1}, R^{Z-2} and R^{Z-3} are identical or different and represent hydrogen, C_1-C_4 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or benzyl,

the cyclic residue R^1 and/or a ring annulated to the cyclic residue formed by R^1 can optionally be substituted by 0 to 2 substituents R^{1-8}, halogen, nitro, amino, cyano and oxo,

wherein

R^{1-8} can independently be selected from the group of C_1-C_4 alkyl, C_1-C_4 alkyloxy, phenyl, phenoxy, phenylamino,

R^2 represents hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_6 aryl, C_5-C_6 cycloalkyl,

and if R^2 is alkyl, R^2 together with the cyclic residue R^1 and D can form a 5- to 6-membered ring,

R^3 represents hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_6 aryl, C_5-C_6 cycloalkyl or a 5-6-membered saturated or unsaturated heterocyclic residue containing up to 2 heteroatoms selected from the group oxygen, nitrogen or sulfur,

which can optionally be substituted by 1 radical R^{3-1},
and wherein R^3 can furthermore be single-foldedly substituted by C_3-C_7 cycloalkyl, C_6 aryl, C_4-C_9 heteroaryl or a heterocyclic residue containing up to 2 heteroatoms selected from the group oxygen, nitrogen or sulfur,
which can be annulated with a phenyl ring,

wherein R^{3-1} represents trifluormethyl, trifluormethoxy, $-OR^{3-2}$, $-SR^{3-2}$, $NR^{3-3}R^{3-4}$, $-NR^{3-2}C(O)OR^{3-3}$, $-CO_2R^{3-5}$, halogen, cyano, nitro or oxo,

wherein R^{3-2} represents hydrogen or C_1-C_4 alkyl,

and wherein R^{3-3} and R^{3-4} are identical or different and represent hydrogen, C_1-C_4 alkyl or benzyl or 9-fluorenylmethyl,

and wherein R^{3-5} represents C_1-C_4 alkyl,

R^4 represents hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 or C_6 aryl,

R^5 represents hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or C_6 aryl,

which can optionally be substituted by 1 radical R^{5-1},

wherein R^{5-1} represents trifluormethyl, trifluormethoxy, $-OR^{5-2}$, $-SR^{5-2}$, $NR^{5-3}R^{5-4}$, halogen, cyano, nitro or oxo,

wherein R^{5-2}, R^{5-3} and R^{5-4} are identical or different and represent hydrogen or C_1-C_4 alkyl,

R^6 represents phenyl or a 5- to 6-membered aromatic heterocyclic residue containing up to 3 heteroatoms independently selected from the group oxygen, nitrogen or sulfur,

and which can optionally be independently substituted by 1 to 3 radicals R^{6-1}

wherein R^{6-1} represents $-NR^{6-2}C(O)NR^{6-3}R^{6-4}$,

wherein R^{6-2} and R^{6-3} are identical or different and represent hydrogen or C_1-C_4 alkyl,

and wherein R^{6-4} represents C_6 aryl,

which can optionally be substituted by 1-2 substituents selected from the group C_1-C_4 alkyl, C_1-C_4 alkyloxy, halogen, nitro, cyano,

or R^3 and R^4 or R^4 and R^5 together form a 5-6-membered saturated or unsaturated ring containing up to 2 nitrogen atoms,

A represents -C(O)-, -SO-, $-SO_2-$,

X represents $-CR^{X-1}R^{X-2}$,

wherein R^{X-1} and R^{X-2} can be independently selected from the group hydrogen, C_1-C_4 alkyl,

Y represents -C(O)-,

D represents -N-,

and pharmaceutically acceptable salts thereof.

In another preferred embodiment, the present invention relates to compounds of general formula (I),

wherein

R^1 represents a 5- to 6-membered saturated, unsaturated or aromatic cyclic residue,

which can contain 0 to 3 heteroatoms selected independently from the group N and S,

wherein the cyclic residue R^1 can be annulated with a 5-membered unsaturated or aromatic cyclic residue, which contains 1 nitrogen atom,

and wherein the cyclic residue R^1 and/or a ring annulated to the cyclic residue R^1 is substituted by 1 to 2 substituents $-R^{1-1}-R^{1-2}-R^{1-3}-Z$, wherein

R^{1-1} represents a bond or C_1 alkyl,

wherein R^{1-1} can optionally be substituted by cyclopentyl,

R^{1-2} represents a bond,

R^{1-3} represents a bond,

Z represents $-C(O)OR^{Z-1}$ or 5-tetrazolyl,

R^{Z-1} represents hydrogen, C_1-C_2 alkyl or benzyl,

the cyclic residue R^1 can optionally be substituted by 0 to 2 substituents R^{1-8}, halogen and nitro,

wherein

R^{1-8} can independently be selected from the group of C_1-C_4 alkyloxy, phenoxy and phenylamino,

R^2 represents hydrogen or C_1-C_3 alkyl,

or

and if R^2 is alkyl, R^2 together with the cyclic residue R^1 and D can form a piperidine ring,

R^3 represents hydrogen or C_1-C_4 alkyl,

which can optionally be substituted by 1 radical R^{3-1},

wherein R^{3-1} represents $NR^{3-3}R^{3-4}$ or $-NR^{3-2}C(O)OR^{3-3}$,

wherein R^{3-2} and R^{3-4} represent hydrogen,

R^{3-3} represents hydrogen, benzyl or 9-fluorenylmethyl,

R^4 represents hydrogen,

R^5 represents hydrogen or C_3 alkyl,

which can optionally be substituted by 1 radical R^{5-1},

wherein R^{5-1} represents $-OR^{5-2}$,

wherein R^{5-2} represents C_1 alkyl,

R^6 represents phenyl,

and which is substituted by 1 radical R^{6-1}

wherein R^{6-1} represents $-NR^{6-2}C(O)NR^{6-3}R^{6-4}$,

wherein R^{6-2} represents hydrogen,

and wherein R^{6-3} represents hydrogen

and R^{6-4} represents C_6 aryl,

which is substituted by 1 substituent C_1 alkyl,

A represents -C(O)-,

X represents $-CR^{X-1}R^{X-2}-$,

wherein R^{X-1} and R^{X-2} represent hydrogen,

Y represents -C(O)-,

D represents N,

and pharmaceutically acceptable salts thereof.

In another preferred embodiment, the present invention relates to compounds of general formula (I),

wherein

R^1 represents phenyl,

and wherein the phenyl is substituted by 1 to 2 substituents $-R^{1-1}-R^{1-2}-R^{1-3}-Z$,

wherein

R^{1-1} represents a bond or C_1 alkyl,

R^{1-2} represents a bond,

R^{1-3} represents a bond,

In another preferred embodiment, the present invention relates to compounds of general formula (I), wherein

Z represents $-C(O)OR^{Z-1}$

R^{Z-1} represents hydrogen, C_1-C_2 alkyl or benzyl,

R^2 represents hydrogen,

R^3 represents hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_6 aryl, C_5-C_6 cycloalkyl or a 5-6-membered saturated or unsaturated heterocyclic residue containing up to 2 heteroatoms selected from the group oxygen, nitrogen or sulfur,

which can optionally be substituted by 1 radical R^{3-1},

and wherein R^3 can furthermore be single-foldedly substituted by C_3-C_7 cycloalkyl, C_6 aryl, C_4-C_9 heteroaryl or a heterocyclic residue containing up to 2 heteroatoms selected from the group oxygen, nitrogen or sulfur,
which can be annulated with a phenyl ring,

wherein R^{3-1} represents trifluormethyl, trifluormethoxy, $-OR^{3-2}$, $-SR^{3-2}$, $-NR^{3-3}R^{3-4}$, $-NR^{3-2}C(O)OR^{3-3}$, $-CO_2R^{3-5}$, halogen, cyano, nitro or oxo,

wherein R^{3-2} represents hydrogen or C_1-C_4 alkyl,

and wherein R^{3-3} and R^{3-4} are identical or different and represent hydrogen, C_1-C_4 alkyl or benzyl or 9-fluorenylmethyl,

and wherein R^{3-5} represents C_1-C_4 alkyl,

R^4 represents hydrogen,

R^5 represents hydrogen,

R^6 represents phenyl,

and which is substituted by 1 radical R^{6-1}

wherein R^{6-1} represents $-NR^{6-2}C(O)NR^{6-3}R^{6-4}$,

wherein R^{6-2} represents hydrogen,

and wherein R^{6-3} represents hydrogen

and R^{6-4} represents C_6 aryl,

which is substituted by 1 substituent C_1 alkyl,

or R^3 and R^4 or R^4 and R^5 together form a 5-6-membered saturated or a unsaturated ring containing up to 2 nitrogen atoms,

A represents -C(O)-,

X represents $-CR^{X-1}R^{X-2}-$,

wherein R^{X-1} and R^{X-2} represent hydrogen,

Y represents -C(O)-,

D represents N,

and pharmaceutically acceptable salts thereof.

In a more preferred embodiment, the present invention relates to compounds of general formula (I),

wherein

R^1 represents phenyl,

which is 1,4-substituted by a substituent $-R^{1-1}-R^{1-2}-R^{1-3}-Z$,

wherein

R^{1-1}, R^{1-2} and R^{1-3} represent bonds.

In another more preferred embodiment, the present invention relates to compounds of general formula (I),
wherein

R^1 represents phenyl,

which is 1,3-substituted by a substituent $-R^{1-1}-R^{1-2}-R^{1-3}-Z$,

wherein

R^{1-1} represents $-CH_2-$,

R^{1-2} and R^{1-3} represent bonds.

In another more preferred embodiment, the present invention relates to compounds of general formula (I),

wherein

R^1 represents a 5-membered heterocycle.

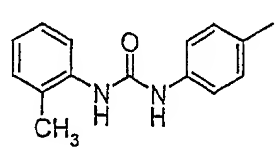
In another more preferred embodiment, the present invention relates to compounds of general formula (I),

wherein

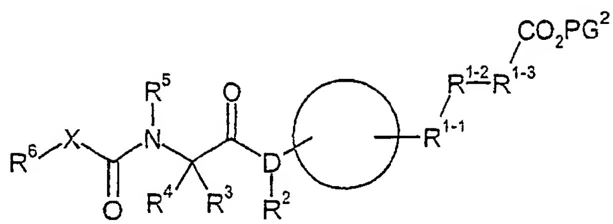
R^1 represents a cyclohexyl ring.

In a very preferred embodiment, the present invention relates to compounds of general formula (I),

wherein R^6 represents

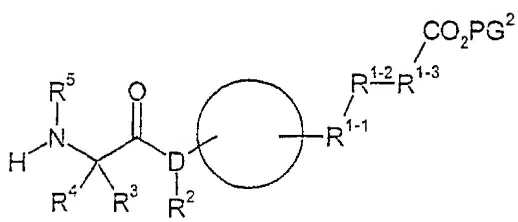


A preferred process for preparation of compounds of general formula (VII)



(VII)

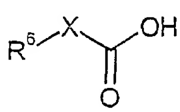
has also been found, which comprises reaction of carboxylic acids of general formula (V)



(V)

or activated derivatives thereof,

with compounds of the general formula (VI)



(VI)

in the presence of a coupling agent and a base in inert solvents, which will be described in more detail in the descriptive part of the specification.

In the context of the present invention alkyl stands for a straight-chain or branched alkyl residue, such as methyl, ethyl, n-propyl, iso-propyl, n-pentyl. If not stated otherwise, preferred is C_1-C_{10} alkyl, very preferred is C_1-C_6 alkyl.

Alkenyl and alkinyl stand for straight-chain or branched residues containing one or more double or triple bonds, e.g. vinyl, allyl, isopropinyl, ethinyl. If not stated otherwise, preferred is C_1-C_{10} alkenyl or alkinyl, very preferred is C_1-C_6 alkenyl or alkinyl.

Cycloalkyl stands for a cyclic alkyl group such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl. Preferred is C_3-C_7 cycloalkyl.

Halogen in the context of the present invention stands for fluorine, chlorine, bromine or iodine. If not specified otherwise, chlorine or fluorine are preferred.

Heteroaryl stands for a monocyclic heteroaromatic system containing 4 to 9 ring atoms, which can be attached via a carbon atom or eventually via a nitrogen atom within the ring, for example, furan-2-yl, furan-3-yl, pyrrol-1-yl, pyrrol-2-yl, pyrrol-3-yl, thienyl, thiazolyl, oxazolyl, imidazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl or pyridazinyl. C_4-C_9 heteroaryl also stands for a 4 to 9-membered ring, wherein one or more of the carbon atoms are replaced by heteroatoms.

A saturated or unsaturated heterocyclic residue stands for a heterocyclic system containing 4 to 9 ring atoms, which can contain one or more double bonds and which can be attached via a ring carbon atom or eventually via a nitrogen atom, e.g. tetrahydrofur-2-yl, pyrrolidine-1-yl, piperidine-1-yl, piperidine-2-yl, , piperidine-3-yl, piperidine-4-yl, piperazine-1-yl, piperazine-2-yl morpholine-1-yl, 1,4-diazepine-1-yl or 1,4-dihydropyridine-1-yl.

If not specified otherwise, in the context of the present invention heteroatom stands preferably for O, S, N or P.

Annulated describes 1,1- or 1,2-fused ring systems, e.g. spiro systems or systems with a [0]-bridge. If not stated otherwise, substituents described for the "parent" ring system (the ring to which the annulated ring is attached) can be also present on the annulated ring.

Derivative stands for a compound that is derived from the parent compound by exchange of one or more hydrogen atoms by other functional groups.

Surprisingly, the compounds of the present invention show good integrin antagonistic activity. They are therefore suitable especially as $\alpha_4\beta_1$ and/or $\alpha_4\beta_7$ and/or $\alpha_9\beta_1$ integrin antagonists and in particular for the production of pharmaceutical compositions for the inhibition or the prevention of cell adhesion and cell-adhesion mediated disorders. Examples are the treatment and the prophylaxis of atherosclerosis, asthma, chronic obstructive pulmonary disease (COPD), allergies, diabetes, inflammatory bowel disease, multiple sclerosis, myocardial ischemia, rheumatoid arthritis, transplant rejection and other inflammatory, autoimmune and immune disorders.

The integrin antagonists of the invention are useful not only for treatment of the physiological conditions discussed above, but are also useful in such activities as purification of integrins and testing for activity.

For the treatment of the above-mentioned diseases, the compounds according to the invention can exhibit non-systemic or systemic activity, wherein the latter is preferred. To obtain systemic activity the active compounds can be administered, among other things, orally or parenterally, wherein oral administration is preferred.

For parenteral administration, forms of administration to the mucous membranes (i.e. buccal, lingual, sublingual, rectal, nasal, pulmonary, conjunctival or intravaginal) or into the interior of the body are particularly suitable. Administration can be carried out by avoiding absorption (i.e. intracardiac, intra-arterial, intravenous, intraspinal or intralumbar administration) or by including absorption (i.e. intracutaneous, subcutaneous, percutaneous, intramuscular or intraperitoneal administration).

For the above purpose the active compounds can be administered per se or in administration forms.

Suitable administration forms for oral administration are, inter alia, normal and enteric-coated tablets, capsules, coated tablets, pills, granules, pellets, powders, solid

and liquid aerosols, syrups, emulsions, suspensions and solutions. Suitable administration forms for parenteral administration are injection and infusion solutions.

The active compound can be present in the administration forms in concentrations of from 0.001 - 100 % by weight; preferably the concentration of the active compound should be 0.5 - 90% by weight, i.e. quantities which are sufficient to allow the specified range of dosage.

The active compounds can be converted in the known manner into the abovementioned administration forms using inert non-toxic pharmaceutically suitable auxiliaries, such as for example excipients, solvents, vehicles, emulsifiers and/or dispersants.

The following auxiliaries can be mentioned as examples: water, solid excipients such as ground natural or synthetic minerals (e.g. talcum or silicates), sugar (e.g. lactose), non-toxic organic solvents such as paraffins, vegetable oils (e.g. sesame oil), alcohols (e.g. ethanol, glycerol), glycols (e.g. polyethylene glycol), emulsifying agents, dispersants (e.g. polyvinylpyrrolidone) and lubricants (e.g. magnesium sulphate).

In the case of oral administration tablets can of course also contain additives such as sodium citrate as well as additives such as starch, gelatin and the like. Flavour enhancers or colorants can also be added to aqueous preparations for oral administration.

For the obtainment of effective results in the case of parenteral administration it has generally proven advantageous to administer quantities of about 0.001 to 100 mg/kg, preferably about 0.01 to 1 mg/kg of body weight. In the case of oral administration the quantity is about 0.01 to 100 mg/kg, preferably about 0.1 to 10 mg/kg of body weight.

It may nevertheless be necessary to use quantities other than those mentioned above, depending on the body weight concerned, the method of administration, the individual response to the active compound, the type of preparation and the time or interval of administration.

Suitable pharmaceutically acceptable salts of the compounds of the present invention that contain an acidic moiety include addition salts formed with organic or inorganic bases. The salt forming ion derived from such bases can be metal ions, e.g., aluminum, alkali metal ions, such as sodium of potassium, alkaline earth metal ions such as calcium or magnesium, or an amine salt ion, of which a number are known for this purpose. Examples include ammonium salts, arylalkylamines such as dibenzylamine and *N,N*-dibenzylethylenediamine, lower alkylamines such as methylamine, *t*-butylamine, procaine, lower alkylpiperidines such as *N*-ethylpiperidine, cycloalkylamines such as cyclohexylamine or dicyclohexylamine, 1-adamantylamine, benzathine, or salts derived from amino acids like arginine, lysine or the like. The physiologically acceptable salts such as the sodium or potassium salts and the amino acid salts can be used medicinally as described above and are preferred.

Suitable pharmaceutically acceptable salts of the compounds of the present invention that contain a basic moiety include addition salts formed with organic or inorganic acids. The salt forming ion derived from such acids can be halide ions or ions of natural or unnatural carboxylic or sulfonic acids, of which a number are known for this purpose. Examples include chlorides, acetates, trifluoroacetates, tartrates, or salts derived from amino acids like glycine or the like. The physiologically acceptable salts such as the chloride salts, the trifluoroacetic acid salts and the amino acid salts can be used medicinally as described below and are preferred.

These and other salts which are not necessarily physiologically acceptable are useful in isolating or purifying a product acceptable for the purposes described below.

The salts are produced by reacting the acid form of the invention compound with an equivalent of the base supplying the desired basic ion or the basic form of the invention compound with an equivalent of the acid supplying the desired acid ion in a medium in which the salt precipitates or in aqueous medium and then lyophilizing. The free acid or basic form of the invention compounds can be obtained from the salt by conventional neutralization techniques, e.g., with potassium bisulfate, hydrochloric acid, sodium hydroxide, sodium bicarbonate, etc.

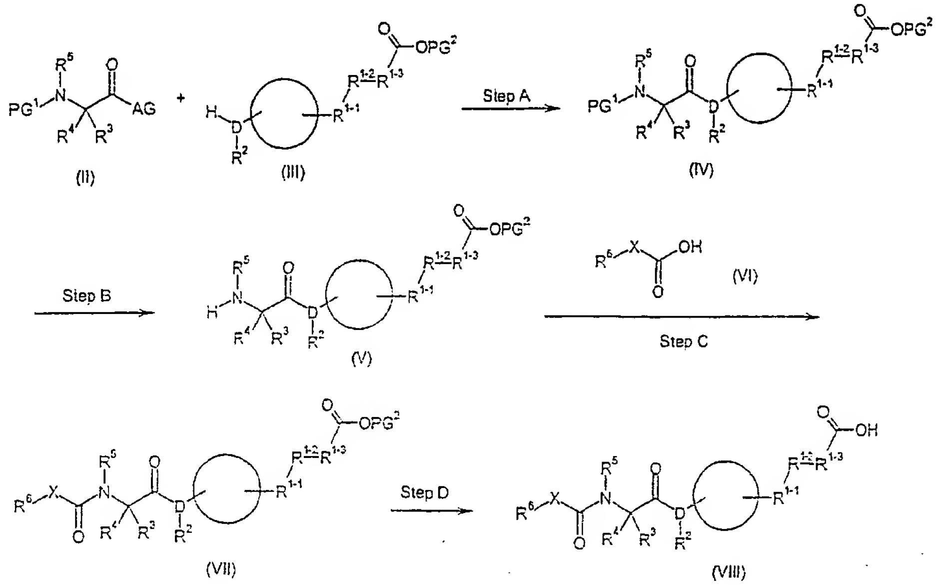
The compounds according to the invention can form non covalent addition compounds such as adducts or inclusion compounds like hydrates or clathrates. This is known to the artisan and such compounds are also object of the present invention.

The compounds according to the invention can exist in different stereoisomeric forms, which relate to each other in an enantiomeric way (image and mirror image) or in a diastereomeric way (image different from mirror image). The invention relates to the enantiomers and the diastereomers as well as their mixtures. They can be separated according to customary methods.

The compounds according to the invention can exist in tautomeric forms. This is known to the artisan and such compounds are also object of the present invention.

General compound synthesis

The synthesis of compounds according to the general formula (I) can be illustrated by the following scheme 1:



Scheme 1

By coupling of the carboxylic acids or activated derivatives (II) with the amines (III) (D = nitrogen), followed by removal of the protecting group PG^1 the amides (V) can be obtained. Coupling with the carboxylic acids (VI) followed by removal of the protecting group PG^2 affords carboxylic acids of type (VIII). Further examples with different A, Y and D groups as defined in formula (I) are described below.

In the above scheme the depicted ring in formulas (III) – (V), (VII) and (VIII) as well as in scheme 3 represents a cyclic moiety formed by R^1. AG stands for hydroxyl or a suitable activating group forming an activated carboxylic acid derivative. Activated carboxylic acids derivatives of this type are known to the person skilled in the art and are described in detail in standard textbooks such as, for example in (i) Houben-Weyl, Methoden der organischen Chemie [Methods of Organic Chemistry], Georg

Thieme Verlag, Stuttgart or (ii) Comprehensive Organic Synthesis, Ed. B. M. Trost, Pergamon Press, Oxford, 1991. The carboxylic acid is preferably activated as mixed anhydride, such as, for example, AG = *iso*-butyl-carbonate; as N-carboxyanhydride (R^5 and AG = –CO–); or by a coupling agents such as, for example dicyclohexyl-carbodiimid (DCC), 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide×HCl (EDCI), 2-(7-aza-3-oxido-1H-1,2,3-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexa-fluorophosphate. Other activated carboxylic acid derivatives such as, for example symmetric anhydrides, halides, or activated esters e.g. succinyl or pentafluorophenyl esters may also be employed.

In the above scheme PG^1 stands for a suitable protecting group of the amino group that is stable under the respective reaction conditions. Protecting groups of this type are known to the person skilled in the art and are described in detail in T. W. Greene, P. G. Wuts, *Protective Groups in Organic Synthesis*, 3rd ed., John Wiley, New York, 1999. The amino group is preferably protected by carbamates, PG^1 being for example *tert*-butyloxycarbonyl (Boc), 9-fluorenylmethyloxycarbonyl (FMOC) or benzyloxy-carbonyl (Cbz- / Z-) or other oxycarbonyl derivatives.

In the above scheme PG^2 stands for a suitable protecting group of the carboxyl group or $COOPG^2$ stands for the carboxylic group attached to a polymeric resin suitable for solid phase synthesis. Protecting groups of this type are known to the person skilled in the art and are described in detail in T. W. Greene, P. G. Wuts, *Protective Groups in Organic Synthesis*, 3rd ed., John Wiley, New York, 1999. The carboxyl group is preferably esterified, PG^2 being C_{1-6}-alkyl such as, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, hexyl, a C_{3-7}-cycloalkyl such as, for example, cyclopropyl, cyclopropylmethyl, cyclobutyl, cyclo-pentyl, cyclohexyl, an aryl such as, for example, phenyl, benzyl, tolyl or a substituted derivative thereof.

Step A

Formation of the amides (IV) can take place by reacting an activated form of the respective carboxylic acid (II), such as a N-carboxyanhydride or an *iso*-butylcarbonate with the desired amine (III) or an acceptable salt thereof.

N-carboxyanhydrides of (II) are commercially available or can be prepared for example by the reaction of the Bis-(N-tert-butyloxycarbonyl) protected derivative of (II) with thionylchloride and pyridine in dimethylformamide or by the reaction of the free amino acid of (II) with phosgene or with phosgene equivalents such as diphosgene, triphosgene or methylchloroformate. *Iso*-butylcarbonates can be prepared in situ by reaction of the N-protected amino acid (II) with *iso*-butylchloroformate as described below. Activated derivatives of the acids (II) such as other anhydrides, halides, esters e.g. succinyl or pentafluorophenyl esters or activated carboxylic acids obtained by the reaction with coupling agents such as, for example dicyclohexylcarbodiimid (DCC), 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide×HCl (EDCI), 2-(7-aza-3-oxido-1H-1,2,3-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate may also be employed.

For example, amides of type (IV) can be prepared as follows:

1) N-carboxyanhydride procedure

A solution/suspension of the amine (III), the N-carboxyanhydride of (II) and catalytic amounts of 4-(N,N'-dimethylamino)pyridine in an inert solvent was refluxed for 0.5-14 days with exclusion of moisture. The product was either isolated by filtration or by aqueous workup employing standard procedures. If necessary the product was purified by trituration or by flash-chromatography or used without further purification.

2) Mixed anhydride procedure

A solution of the carboxylic acid derivative (II) and of N-methylmorpholine in an inert solvent was cooled to -15°C and *iso*-butyl chloroformate was added and stirred at 0°C. The amine (III) in an inert solvent was added at -15°C. The solution was stirred at 0°C, and at r.t. and was evaporated. The residue was redissolved in ethyl acetate, washed with aqueous acid and base, dried and evaporated. If necessary the product was purified by trituration or by flash-chromatography or used without further purification.

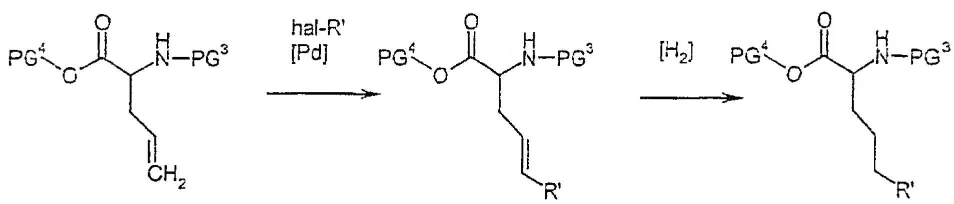
Compounds of general formula (II) are commercially available, known or can be prepared by customary methods starting from known α-amino acids or precursors for customary α-amino acid synthesis. For the preparation process according to the invention, the amino group is in this case blocked by a conventional protective group PG^1.

In the α-position to the carboxyl group, these carboxylic acid derivatives can have substituents such as described under R^3 and R^4, for example, hydrogen, a C_1-C_{10}-alkyl, a C_3-C_7-cycloalkyl, an aryl, an alkenyl residue, or an alkinyl residue. The alkyl, alkenyl and cycloalkyl residues and the benzyl residue can be introduced by reaction of the ester of the starting compounds with the appropriate alkyl, alkenyl, cycloalkyl or benzyl halides in basic medium, if the corresponding derivatives are not commercially available. The alkinyl residue can be introduced, for example, by reaction of the bromo ester of the present starting compound with an appropriate acetylide anion. In the case of the phenyl residue the starting materials used are preferably the corresponding α-phenyl-α-aminocarboxylic acid derivatives and, if necessary, the other substituents at the α-C atom to the terminal carboxyl group are introduced via the appropriate alkyl halide.

The above reactions and their implementation are well known to the person skilled in the art and are described in detail in standard textbooks such as, for example, in (i)

Houben-Weyl, Methoden der organischen Chemie [Methods of Organic Chemistry], Georg Thieme Verlag, Stuttgart or Stuttgart or (ii) Comprehensive Organic Synthesis, Ed. B. M. Trost, Pergamon Press, Oxford, 1991.

If the substituents themselves should be substituted, e.g. by R', appropriate reactive groups should be present in the substituent to allow further functionalization. These reactive groups should be inert to the reaction conditions of the previous step. For this purpose, the substituent can also be unsaturated to allow further functionalization such as palladium catalyzed C-C-coupling reactions (e.g. Heck-reaction or Sonogashira-reaction), eventually followed by hydrogenation (scheme 2):



Scheme 2

In the abovementioned scheme PG^4 stands for a protecting group of the carboxyl group as described under PG^2, hal stands for a leaving group such as a halogen, tosyl, mesyl or triflate, [Pd] stands for a Palladium(0) or Palladium(II) moiety. PG^3 stands for a protecting group of the amino group such as described under PG^1. Protecting groups of this type are known to the person skilled in the art and are described in detail in T. W. Greene, P. G. Wuts, *Protective Groups in Organic Synthesis*, 3rd ed., John Wiley, New York, 1999.

If the substituent R^3 or R^4 in the α-position to the carboxylic group carry an appropriate substituted aryl or heteroaryl unit, another method for insertion of an additional substituent are the C-C-coupling reactions as described under the synthesis of precursors (VI).

Compounds of general formula (III) are commercially available, known or can be prepared by customary methods starting from known carboxylic acid derivatives.

In case R^{1-1}, R^{1-2} and/or R^{1-3} are methylen groups, the carbon chain can be elongated by Arndt-Eistert-reaction and optionally be derivatized by common methods for α-derivatization of carboxylic acids such as nucleophilic substitution.

In case, Y is different from carbonyl and/or D is different from nitrogen - as defined in formula (I) - the respective compounds (IV) can be prepared as follows:

For example, in case Y and D form an sulfinamide, or sulfonamide, they may be prepared by reacting the respective sulfinylchlorides or sulfonylchlorides with the desired amine (III) or an acceptable salt thereof.

For example, in case Y and D form an ether or thioether, the O-C or S-C- bonds are formed via alkylation of the corresponding alcohols or thiols with alkylating agents such as alkyl halides, alkyl tosylates and the like. The thioether can be converted into the corresponding sulfoxides or sulfones by oxidation with reagents like mCPBA or hydrogen peroxide.

In case Y and D form a carbon-nitrogen-bond or a nitrogen-carbon-bond, the bond is established by reductive amination via the corresponding aldehyde or ketone and the corresponding amine in the presence of a reducing agent such as sodium cyanoborohydride. In the case Y and D form a carbon-nitrogen bond in which the nitrogen atom is attached to an aromatic ring, the amine group -Y-NR^2H can be coupled to the aromatic ring by an Buchwald reaction employing an halogen or triflate substituted aromatic residue and a suitable catalyst such as, for example Pd(0) or Pd(II) with phospine ligands such as triphenylphosphine, 2,2'-bis-(diphenylphosphino)-1,1'-binaphthyle (BINAP) or 1,1'-bis-(diphenylphosphino)ferrocene (dppf) together with an appropriate base such as, for example cesium carbonate or cesium fluoride.

In case Y and D form a carbon-carbon-bond, the bond may be established by Wittig reaction of the corresponding ketone or aldehyde and the corresponding phosphonium ylide followed by reduction of the double bond, e.g. by catalytic hydrogenation.

In case Y is carbonyl and D is a carbon moiety, the bond may be formed by a Grignard type reaction of the corresponding aldehyde of Y and the corresponding Grignard-reagent of D, followed by the oxidation of the resulting alcohol to the ketone, e.g. by Swern-oxidation or Jones-oxidation.

The above reactions and their implementation are well known to the person skilled in the art and are described in detail in standard textbooks such as, for example, in (i) Houben-Weyl, Methoden der organischen Chemie [Methods of Organic Chemistry], Georg Thieme Verlag, Stuttgart Stuttgart or (ii) Comprehensive Organic Synthesis, Ed. B. M. Trost, Pergamon Press, Oxford, 1991.

When more than one choice of reaction methods exist, the person skilled in the art is able to choose the appropriate pathway according to selectivity and possible use of protecting groups such as described in T. W. Greene, P. G. Wuts, *Protective Groups in Organic Synthesis*, 3rd ed., John Wiley, New York, 1999.

Step B

The removal of protecting group PG^1 can be performed, depending on the nature of PG^1, either by an acid such as trifluoroacetic acid (for example in the case PG^1 is tert-butyloxycarbonyl (Boc)), a base such as piperidine (for example in the case PG^1 is 9-fluorenylmethyloxycarbonyl (FMOC)) or by catalytic hydrogenation (for example in the case PG^1 is benzyloxycarbonyl (Cbz- / Z-)).

Step C

Formation of the amides (VII) can take place by reacting the respective carboxylic acids (VI) - activated by a coupling agent such as DCC and HOBt; EDCI and HOBt or HATU - with the desired amines (V) or an acceptable salt thereof. Activated derivatives of the acids (VI) such as anhydrides, halides, and esters e.g. succinyl or pentafluorophenyl esters may also be employed.

For example, amides (VII) can be prepared as follows:

A solution of carboxylic acid, HOBt and EDCI in an inert solvent is stirred at r.t.. After addition of the amine and a non-nucleophilic base such as ethylisopropylamine stirring is continued at r.t. or elevated temperature. The reaction mixture is poured into water and worked up by standard procedures.

Compounds of general formula (VI) are commercially available, known or can be prepared by customary methods starting from known carboxylic acid derivatives.

For example, biphenyl substituted acetic acid derivatives can be prepared by means of an aryl-aryl coupling of the respective phenyl acetic acid derivatives and a suitable phenyl system.

Possible coupling reactions are, for example, the reaction of two unsubstituted phenyl groups in the presence of $AlCl_3$ and an acid (Scholl reaction), the coupling of the two phenyl iodides in the presence of copper (Ullmann reaction), the reaction of the unsubstituted carboxylic acid derivative with a phenyldiazonium compound under basic conditions (Gomberg-Bachmann reaction) or coupling with participation of organometallic reagents such as coupling of a phenyl halide with an organometallic phenyl compound in the presence of a palladium compound, for example a Pd(0), a Pd(II) or a Pd(IV) compound, and of a phosphane such as triphenylphosphane (e.g. Suzuki reaction).

Bisarylureas can be prepared by coupling of an amino phenyl acetic acid derivative and a phenylisocyanate. Bisarylamides can be prepared by coupling of an amino phenyl acetic acid and an activated benzoic acid derivative such as described under Step A. Bisarylcarbamates can be prepared by coupling of an isocyanato phenyl acetic acid ester and a phenol derivative followed by saponification as described in Step D.

In case, A - as defined in formula (I) - is different from carbonyl, the respective compounds (IV) can be prepared as follows:

For example, in case A forms a sulfinamide, sulfonamide, they may be prepared as described under Step A. Oxalic amides can be prepared by the same means as the amides described above. Phosphinic acid amides and phosphonic acid amides can be prepared by coupling of activated phosphinic/phosphonic acids with amines (V). In case A is a heteroaromatic or aromatic system, the respective compounds (IV) can be prepared by nucleophilic substitution of the respective fluorosubstituted systems with a suitable amine (V).

Step D

The removal of the protecting group PG^2 can be performed either by an acid such as trifluoroacetic acid or an base such as potassium hydroxide or lithium hydroxide, depending on the nature of PG^2. Reactions are carried out in aqueous, inert organic solvents such as alcohols e.g. methanol or ethanol, ethers e.g. tetrahydrofurane or dioxane or polar aprotic solvents e.g. dimethylformamide. If necessary, mixtures of the above solvents may be used.

In case PG^2 stands for polymeric resin, the removal can take place using strong acid such as trifluoroacetic acid in dichloromethane.

Examples

Abbreviations

AcOH	acetic acid
Boc	tert-butyloxycarbonyl
DCC	dicyclohexylcarbodiimid
GC	gas chromatography
DIPEA	diisopropylethylamine
EDCI	1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide×HCl
eq.	equivalents
FC	flash chromatography
HATU	2-(7-aza-3-oxido-1H-1,2,3-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HOBt	N-hydroxybenzotriazole monohydrate
HPLC	high performance liquid chromatography
ICAM-1	intracellular adhesion molecule 1
IL-1	interleukin 1
LPS	lipopolysaccharide
MAdCAM-1	mucosal addressin cell adhesion molecule 1
MeOH	methanol
min.	minutes
M.p.	melting point
NF-κB	nuclear factor κB
NMR	nuclear magnetic resonance
n.d.	not determined
r.t.	room temperature
R_f	TLC: R_f value = distance spot traveled / distance solvent front traveled
TFA	trifluoroacetic acid
THF	tetrahydrofurane
TLC	thin layer chromatography

TNF-α	tumor necrosis factor α
t_R	retention time determined by HPLC
VCAM-1	vascular cell adhesion molecule 1
VLA-4	very late antigen 4 ($\alpha_4\beta_1$ integrin)

General remarks

In the examples below, all quantitative data, if not stated otherwise, relate to percentages by weight.

Flash chromatography was carried out on silica gel 60, 40–63µm (E. Merck, Darmstadt, Germany).

Thin layer chromatography was carried out, employing silica gel 60 F_{254} coated aluminum sheets (E. Merck, Darmstadt, Germany) with the mobile phase indicated.

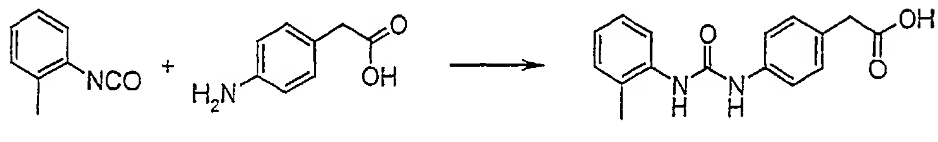
Melting points were determined in open capillaries and are not corrected.

All retention times are indicated in minutes and, if not stated otherwise, were determined by high-performance liquid chromatography (HPLC) by means of UV detection at 210 / 250 nm and a flow rate of 1 ml/min. An acetonitrile/water mixture with 0.1% trifluoroacetic acid (vol./vol.) was used as eluent with a linear gradient of: 0 min. = 0% acetonitrile, 25 min. = 100% acetonitrile, 31 min = 100 % acetonitrile, 32 min 0% acetonitrile, 38 min 0% acetonitrile. Two methods were used: for method A a LiChrospher 100 RP-18, 5 µm, 250×4mm (E. Merck, Darmstadt, Germany) column and for method B a Purospher RP-18e, 5µm, 250×4mm (E. Merck, Darmstadt, Germany) column was used.

The mass determinations were carried out using the electron spray ionization (ESI) method employing loop injection or split injection via a HPLC system.

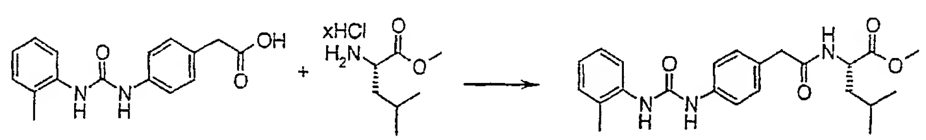
Precursor synthesis

Example I: 2-{4-[(2-Toluidinocarbonyl)amino]phenyl}acetic acid



To a solution of 2-(4-aminophenyl)acetic acid (108.8 g, 0.72 mol) in CH_2Cl_2 (1.0 l) and triethylamine (120 ml) was added a solution of 2-methylphenyl isocyanate (90.5 ml, 0.72 mol) in CH_2Cl_2 (500 ml) dropwise at r.t.. After stirring for 18 h at r.t., water (2.5 l) and CH_2Cl_2 (2.0 l) were added and the layers were separated. The organic layer was extracted with water (3 × 400 ml). The combined aqueous layers were concentrated to 3.0 l and acidified to pH 2 by the addition of concentrated aqueous HCl. The precipitate was collected by filtration, washed with cold water and dried in an exsiccator over concentrated H_2SO_4 affording 166.5 g (82%) white solid. M.p. 205-206°C; TLC (CH_2Cl_2/MeOH 9:1): R_f 0.14. ^{1}H-NMR (400 MHz, D_6-DMSO): 12.21 (br s, 1H), 9.11 (s, 1H), 8.00 (s, 1H), 7.83 (d, 7.6 Hz, 1H), 7.40 (d, 8.5 Hz, 2H), 7.17-7.12 (m, 4H), 6.96-6.92 (m, 1H), 3.48 (s, 2H), 2.24 (s, 3H).

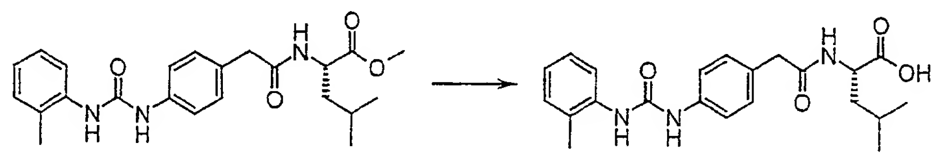
Example II: 2-{4-[(2-Toluidinocarbonyl)amino]phenyl}acetyl-L-leucine methyl ester



A solution of 2-{4-[(2-toluidinocarbonyl)amino]phenyl}acetic acid (1.96 g, 6.89 mmol), HOBt (1.16 g, 7.58 mmol) and EDCI in 70 ml dimethylformamide was stirred 90 min at r.t.. After addition of L-leucine methyl ester hydrochloride (1.25 g, 6.89 mmol) in dimethylformamide (20 ml) and ethyldiisopropylamine (5.75 ml, 34.5 mmol) stirring at r.t. was continued for 18 h. The reaction mixture was poured into water (350 ml) and extracted with ethyl acetate (4×150 ml). The combined organic layers were washed with 0.1 N aqueous HCl, saturated aqueous Na_2CO_3, brine, dried ($MgSO_4$) and evaporated. Yield: 2.49 g (88%) white solid. M.p. 166-168°C; TLC

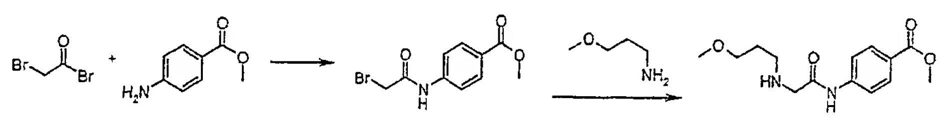
(CH_2Cl_2/MeOH 9:1): R_f 0.56; ^{1}H-NMR (400 MHz, D_6-DMSO): 8.96 (s, 1H), 8.42 (d, 7.7 Hz, 1H), 7.89 (s, 1H), 7.84 (d, 7.44 Hz, 1H), 7.38 (d, 8.5 Hz, 2H), 7.18-7.11 (m, 4H), 6.96 (m, 1H), 4.30-4.23 (m, 1H), 3.61 (m, 3H), 3.43-3.36 (m, 2H), 2.24 (s, 3H), 1.67-1.45 (m, 3H), 0.89 (d, 6.4 Hz, 3H), 0.82 (d, 6.4 Hz, 3H).

Example III:2-{4-[(2-toluidinocarbonyl)amino]phenyl}acetyl-L-leucine



A solution of 2-{4-[(2-toluidinocarbonyl)amino]phenyl}acetyl-L-leucine methyl ester (2.42 g, 5.88 mmol) and KOH (3.30 g, 58.75 mmol) in methanol/water 1:1 (180 ml) was stirred at 50°C for 5 h. After washing with methyl-tert-butylether (80 ml) the volume of the reaction mixture was reduced until a slight turbidity was observed. The solution was acidified to pH 2 by the addition of 1 N aqueous HCl. The precipitate was collected by filtration, washed with cold water and dried in vacuum. Yield: 1.75 g (72 %) white solid. M.p.: 178-179°C, TLC (CH_2Cl_2/MeOH/AcOH 9:1:0.1): R_f 0.16; ^{1}H-NMR (400 MHz, D_6-DMSO): 12.51 (br s, 1H), 9.00 (s, 1H), 8.25 (d, 8.0 Hz, 1H), 7.93 (s, 1H), 7.83 (d, 7.5 Hz, 1H), 7.36 (d, 8.5 Hz, 2H), 7.17-7.12 (m, 4H), 6.95-6.91 (m, 1H), 4.23-4.17 (m, 1H), 3.43-3.32 (m, 2H), 2.24 (s, 3H), 1.68-1.46 (m, 3H), 0.89 (d, 6.5 Hz, 3H), 0.82 (d, 6.5 Hz, 3H).

Example IV: Methyl 4-({[(3-methoxypropyl)amino]acetyl}amino)benzoate

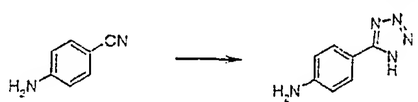


To a solution of methyl 4-aminobenzoate (10.0 g, 66.2 mmol) and triethylamine (10.1 ml, 72.8 mmol) in dichloromethane (100 ml) was added a solution of bromoacetylbromide (6.34 ml, 72.8 mmol) in dichloromethane (30 ml) at 0°C. After stirring for 18 h at room temperature and 18 h under reflux the reaction mixture was concentrated under vacuum. The residue was taken up in ethyl acetate, washed with 1 N aqueous HCl and water, dried over $MgSO_4$ and evaporated. Yield 15.8 g (88%)

of methyl 4-[(bromoacetyl)amino]benzoate as a pale brown solid. M.p.: 144-146°C, TLC (hexane/ethyl acetate 1:1): R_f 0.46.

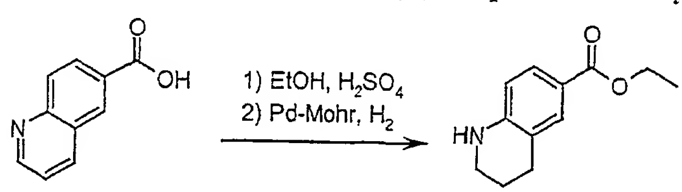
To a solution of methyl 4-[(bromoacetyl)amino]benzoate (2.72 g, 10.0 mmol) in dimethylformamide (20 ml) was added 3-methoxypropylamine (1.78 g, 20.0 mmol) and triethylamine (22.3 ml, 160 mmol). After stirring at room temperature for 18 h, the reaction mixture was concentrated under vacuum and purified by flash chromatography (CH_2Cl_2/MeOH 9:0.4) affording 1.81 g (65%) of methyl 4-({[(3-methoxypropyl)amino]acetyl}amino)benzoate as a pale red solid.

Example V: 4-(1H-tetraazol-5-yl)aniline



To a solution of 4-aminobenzonitrile (11.8 g, 100 mmol) and triethylamine hydrochloride (17.9 g, 130 mmol) in toluene (550 ml) was added sodium azide (8.45 g, 130 mmol). After stirring for 24 h at 95°C, the reaction mixture was cooled to room temperature and was extraced with water (3×60 ml). The combined aqueous phases were acidified with concentrated aqueous HCl to pH 2-3. The product was collected by filtration, washed with water and dried in vacuum. Yield 9.59 g (60%) pale brown solid. M.p.: 280-281°C, TLC (CH_2Cl_2/MeOH/AcOH 9:1:0.1): R_f 0.30

Example VI: Ethyl 1,2,3,4-tetrahydro-6-quinolinecarboxylate

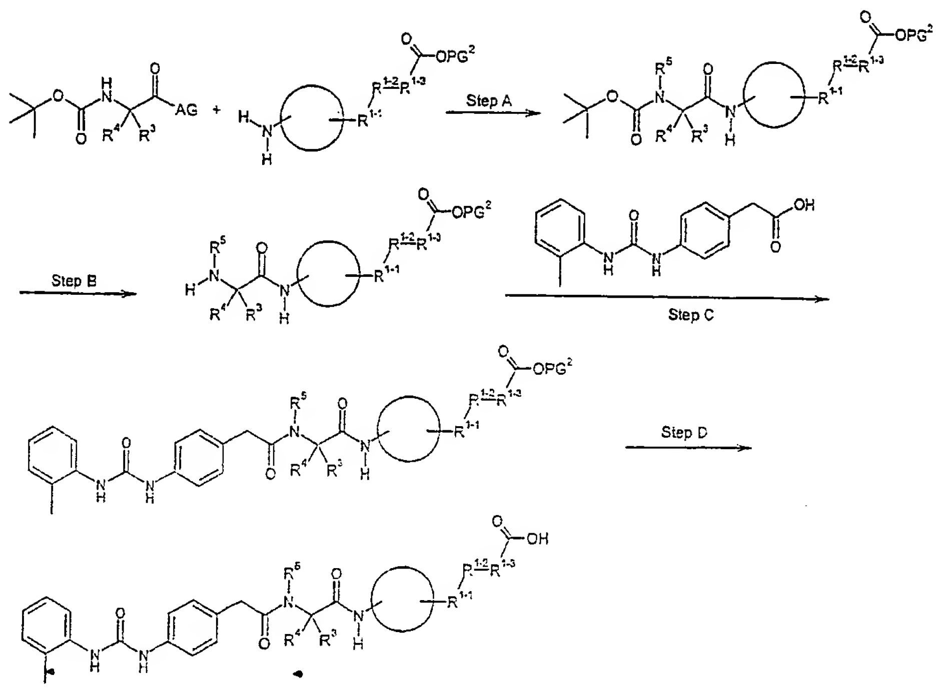


A solution of 6-quinolinecarboxylic acid (9.50 g, 54.9 mmol) and 2 ml of concentrated sulfuric acid in ethanol (250 ml) was refluxed for 8 h. The solvent was evaporated and the residue was taken up in water. After adjustment of the pH to 8 by the addition of potassium hydroxide the product was collected by filtration and dried in

vacuum. Yield 9.85 g (89%) of ethyl 6-quinolinecarboxylate as a pale brown solid. M.p.: 66-67°C, TLC (CH_2Cl_2/MeOH/AcOH 9:0.5:0.1): R_f 0.52

A solution of ethyl 6-quinolinecarboxylate (9.80 g, 48.7 mmol) was acidified to pH 2 by the addition of 1N aqueous HCl. After addition of 20% Pd-Mohr catalyst (1.96 g) the solution was hydrogenated at 60°C under 3 bar of hydrogen pressure for 17 h. The reaction mixture was filtered through celite. The filtrate was evaporated and the residue was taken up in ethyl acetate and water. The pH was adjusted to 10 by the additon of 1 N aqueous potassium hydroxide. The phases were separated and the organic phase was washed with brine, dried over Na_2SO_4 and evaporated. Yield 8.72 g (87%) of ethyl 1,2,3,4-tetrahydro-6-quinolinecarboxylate as a pale brown solid. M.p.: 68-70°C, GC-MS: [M^+] = 205.

Compound synthesis



Scheme 3

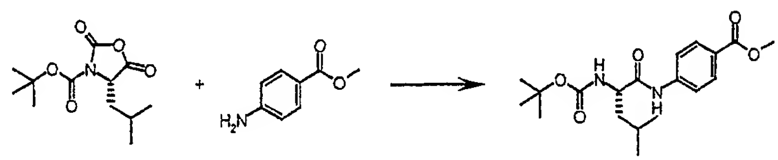
Step A:

General procedure A1 (GP A1): Coupling of amines with Boc-L-leucin-N-carboxy-anhydride:

A solution/suspension of 1.0 eq. of the amine, 1.0 eq. of Boc-L-leucin-N-carboxyanhydride and 0.3 eq. of 4-(N,N'-dimethylamino)pyridine was refluxed for 0.5 – 14 days with exclusion of moisture. If a precipitate was formed, the precipitate (product) was collected by filtration. The reaction mixture / filtrate was evaporated to dryness, redissolved in ethyl acetate and washed with 1 N aqueous HCl, saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$ and evaporated. Both solids were combined.

If necessary the product was purified by trituration or by flash-chromatography or used without further purification.

Example 1: Methyl 4-({Boc-L-leucine}amino)benzoate

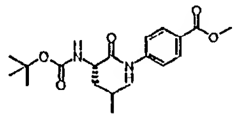
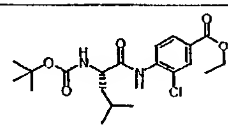
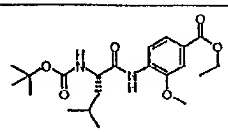
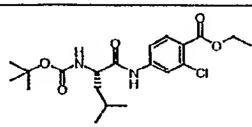
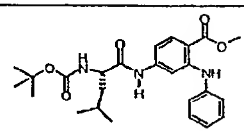


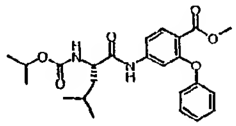
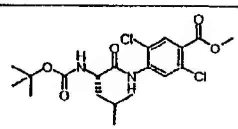
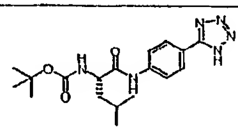
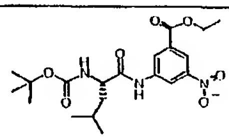
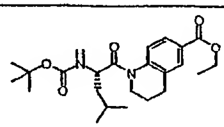
Methyl 4-aminobenzoate (0.75 g, 4.97 mmol) was dissolved in CH_2Cl_2 (7 ml). After the addition of Boc-L-leucin-N-carboxyanhydride (1.28 g, 4.79 mmol) and 4-(N,N'-dimethylamino)pyridine (180 mg, 1.49 mmol) the solution was stirred under reflux for 4 days. The precipitate (product) was collected by filtration. The filtrate was evaporated to dryness, redissolved in ethyl acetate and washed with 1 N aqueous HCl, saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$ and evaporated. Combined Yield: 1.35 (75%) white solid.

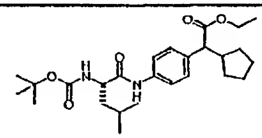
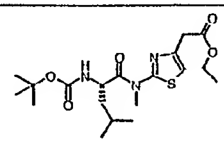
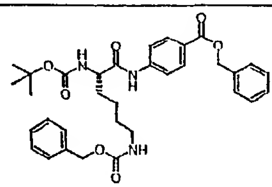
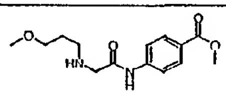
General procedure A2 (GP A2): Coupling of amines with carboxylic acids activated by *iso*-butyl chloroformate.

A solution of 1.0 eq. of the carboxylic acid derivative and 1.0 eq. of N-methylmorpholine in tetrahydrofurane was cooled to -15°C and 1.0 eq. of *iso*-butyl chloroformate was added dropwise. After 5 min at 0°C, 1.0 eq. of the amine in tetrahydrofurane was added at -15°C. The solution was stirred for 1 h at 0°C, 1-4 d at r.t. and was evaporated. The residue was redissolved in ethyl acetate, washed with 1 N aqueous HCl (2x), saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$ and evaporated.

Table 1: Characterization of reaction products according to Step A

Example No.	Structure	Procedure	Yield [%]	Product	R_f	M.p. [°C]	ESI-MS	HPLC t_R[min]
1		GP A1	75	white solid	0.52 (CH_2Cl_2/MeOH 9:0.1)	72 - 73	309.1 $[M+H]^+$	n.d.
2		GP A1, FC: CH_2Cl_2/MeOH 9:0.3- 8:2	31	white solid	0.68 (petrol ether / ethyl acetate 8:2)	n.d.	413.4 $[M+H]^+$	27.5 Method B
3		GP A1, crude product	42	pale red solid	0.60 (petrol ether / ethyl acetate 6:4)	n.d.	409.1 $[M+H]^+$	25.4 Method B
4		GP A1, crude product	39	pale brown oil	0.30 (petrol ether / ethyl acetate 8:2)	n.d.	399.0 $[M+H]^+$	25.4 Method B
5		GP A1, crude product	32	white solid	0.46 (petrol ether / ethyl acetate 8:2)	207 - 209	456.1 $[M+H]^+$	27.8 Method B

Example No.	Structure	Procedure	Yield [%]	Product	R_f	M.p. [°C]	ESI-MS	HPLC t_R[min]
6		GP A1, crude product	52	white solid	0.70 (petrol ether / ethyl acetate 8:2)	n.d.	457.1 $[M+H]^+$	26.0 Method B
7		GP A1, crude product	37	pale brown solid	0.84 (petrol ether / ethyl acetate 6:4)	n.d.	431.0 $[M-H]^-$	27.1 Method B
8		GP A1 (aq. $NaHCO_3$ wash omitted) crude product	39	pale brown solid	0.62 (CH_2Cl_2/MeOH/AcOH 9:1:0.1)	n.d.	373.1 $[M-H]^-$	21.3 Method A
9		GP A1, crude product	46	pale yellow solid	0.80 (petrol ether / ethyl acetate 1:1)	n.d.	424.1 $[M+H]^+$	25.9 Method B
10		GP A1, FC: petrol ether/ethyl acetate 9:0.3 – 9:1	3	yellow oil	0.52 (petrol ether / ethyl acetate 1:1)	n.d.	419 $[M+H]^+$	n.d.

Example No.	Structure	Procedure	Yield [%]	Product	R_f	M.p. [°C]	ESI-MS	HPLC t_R[min]
11		GP A2, FC: petrol ether/ethyl acetate 9:1	17	pale yellow solid	0.90 (petrol ether / ethyl acetate 6:4)	n.d.	461.5 $[M+H]^+$	n.d.
12		GP A2, crude product	89	pale yellow oil	0.83 (CH_2Cl_2/MeOH/AcOH 9:1:0.1)	n.d.	414.3 $[M+H]^+$	25.3 Method B
13		GP A2, FC: petrol ether/ethyl acetate 10:1 – 6:4	35	white solid	0.36 (petrol ether / ethyl acetate 6:4)	50 - 52	590.4 $[M+H]^+$	n.d.
14		as described in the precursor synthesis	65%	pale red solid	0.36 (CH_2Cl_2/MeOH 9:1)	49 - 50	281.0 $[M+H]^+$	n.d.

Step B:

General procedure B (GP B): Cleavage of the Boc-protecting group with trifluoro-acetic acid

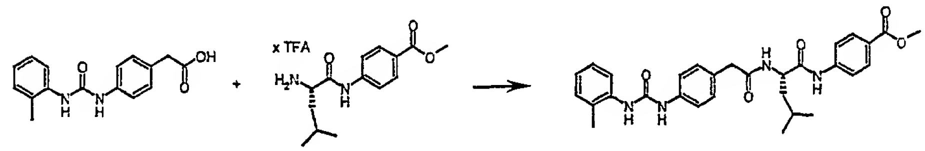
To a solution of the Boc-protected amine was added 20 vol% trifluoroacetic acid in dichloromethane at 0°C. Stirring was continued at room temperature for 0.5-24 h. The solvent was removed at room temperature under reduced pressure. The residue was coevaporated twice with dichloromethane, dried under high vacuum and subjected to the reaction step C without further purification.

Step C:

General procedure (GP C1): Coupling of amines with 2-{4-[(2-toluidinocarbonyl)-amino]phenyl}acetic acid:

A solution of 1.0 eq. 2-{4-[(2-toluidinocarbonyl)amino]phenyl}acetic acid, 1.1 eq. HOBt and 1.1 eq. EDCI in DMF was stirred for 2 h at r.t.. After addition of 1.0 eq. amine e.g. as TFA salt and 3 – 9 eq. ethylisopropylamine stirring was continued for 18 h at r.t.. The reaction mixture was poured into the 4-fold amount of water. The precipitate was collected by filtration, washed with cold water and dried in vacuum. If necessary the product was purified by trituration or by flash-chromatography.

Methyl 4-([({4-[(2-toluidinocarbonyl)amino]phenyl}acetyl)L-leucin]amino)benzoate



Methyl 4-[(L-leucin)amino]benzoate trifluoroacetate (3.81 g, 10.1 mmol) was reacted according to GP C1 in a total volume of 60 ml of dimethylacetamide. Trituration

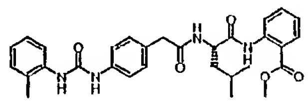
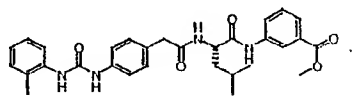
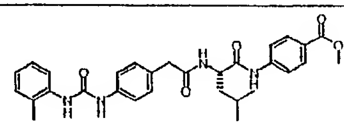
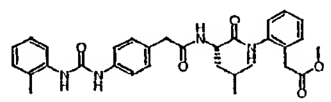
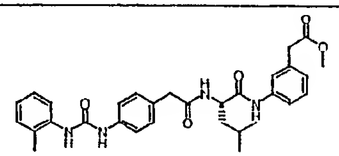
with CH_2Cl_2 yielded 4.78 g (90%) pale brown solid. M.p. 250-252°C, TLC (AcOH:MeOH:CH_2Cl_2 0.1:0.5:9): R_f 0.46; ^{1}H-NMR (400 MHz, D_6-DMSO):10.47 (s, 1H), 8.96 (s, 1H), 8.39 (d, 7.7 Hz, 1H), 7.93-7.89 (m, 3H), 7.83 (d, 7.8 Hz, 1H), 7.75 (d, 8.8 Hz, 2H), 7.37 (d, 8.4 Hz, 2H), 7.18-7.12 (m, 4 H), 6.95-6.92 (m, 1H), 4.49 – 4.43 (m, 1H), 3.82 (s, 3H), 3.47 – 3.38 (m, 2H), 2.24 (s, 3H), 1.66 – 1.50 (m, 3H), 0.92 (d, 6.4 Hz, 3H), 0.86 (d, 6.4 Hz, 3H); ESI-MS: 531.3 $[M+H]^+$.

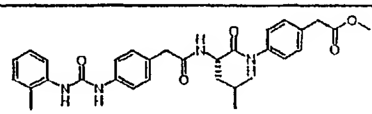
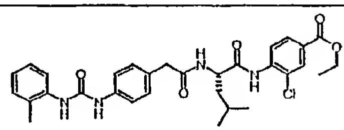
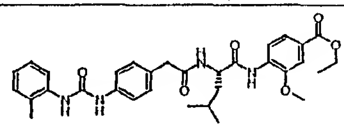
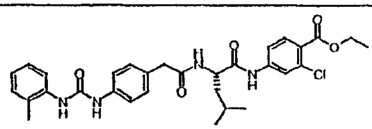
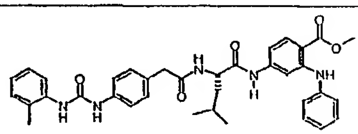
General procedure (GP C2): Coupling of amines with 2-{4-[(2-toluidinocarbonyl)amino]phenyl}acetyl-L-leucine

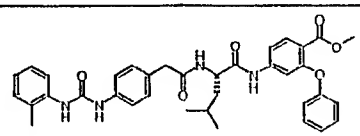
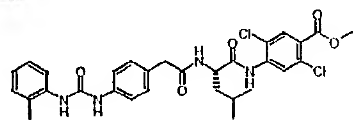
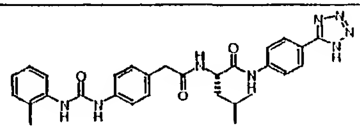
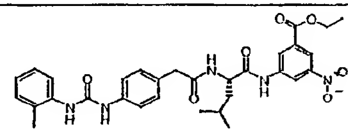
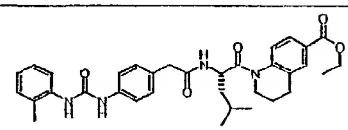
In several cases it is advisable to couple the amine (III) directly with with 2-{4-[(2-toluidinocarbonyl)amino]phenyl}acetyl-L-leucine followed by the cleavage of the protecting group PG^2, thus omitting steps A and B:

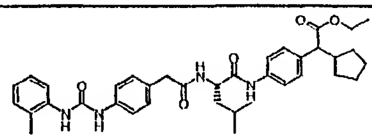
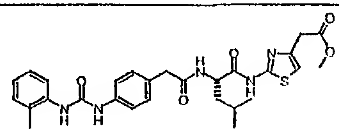
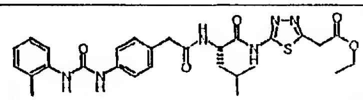
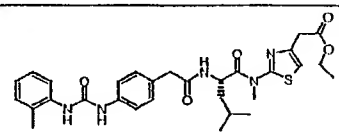
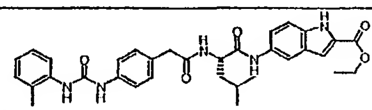
A solution of 1.0 eq. 2-{4-[(2-toluidinocarbonyl)amino]phenyl}acetyl-L-leucine, 1.1 eq. HOBt and 1.1 eq. EDCI in DMF was stirred for 2 h at r.t.. After addition of 1.0 eq. amine (as free amino or as a salt) and 3-9 eq. ethylisopropylamine stirring was continued for 18 h at r.t.. The reaction mixture was poured into the 4-fold amount of water. The precipitate was collected by filtration, washed with cold water and dried in vacuum. If necessary the product was purified by trituration or by flash-chromatography.

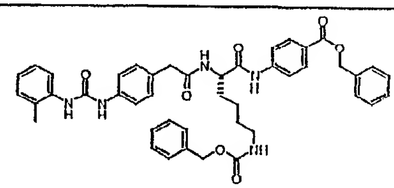
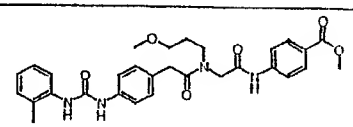
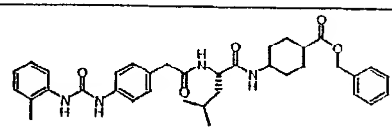
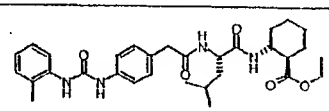
Table 2 The following examples were prepared by subsequently applying the general procedures B & C1/C2 as indicated.

Example No.	Structure	Procedure	Yield [%]	Product	R_f	M.p. [°C]	ESI-MS	HPLC t_R[min]
15		GP C2	–	–	–	170	–	n.d.
16		GP C2	–	–	–	220	–	n.d.
17		1) GP B 2) GP C1, 9 eq. DIPEA	90	pale brown solid	0.46 (CH_2Cl_2/MeOH/AcOH 9:0.5:0.1)	250 - 252	531.3 $[M+H]^+$	26.6 Method A
18		GP C2	–	–	–	218	–	n.d.
19		GP C2	–	–	–	200	–	n.d.

Example No.	Structure	Procedure	Yield [%]	Product	R_f	M.p. [°C]	ESI-MS	HPLC t_R[min]
20		GP C2	–	–	–	222	–	n.d.
21		1) GP B 2) GP C1, 9 eq. DIPEA	81	pale brown solid	0.74 (CH_2Cl_2/MeOH/AcOH 9:1:0.1)	163 - 165	579.3 $[M+H]^+$	25.5 Method B
22		1) GP B 2) GP C1, 3) 9 eq. DIPEA	81	pale brown solid	0.34 (CH_2Cl_2/MeOH/AcOH 9:1:0.1)	139 - 141	575.0 $[M+H]^+$	24.5 Method A
23		1) GP B 2) GP C1: 1.1 eq. HATU (no EDCI, HOBt) & 5 eq. DIPEA	66	white solid	0.74 (CH_2Cl_2/MeOH 9:1)	181 - 184	564.5 $[M+H]^+$	24.0 Method A
24		1) GP B 2) GP C1, 9 eq. DIPEA	90	pale brown solid	0.34 (CH_2Cl_2/MeOH/AcOH 9:0.5:0.1)	205 - 206	622.2 $[M+H]^+$	26.1 Method B

Example No.	Structure	Procedure	Yield [%]	Product	R_f	M.p. [°C]	ESI-MS	HPLC t_R[min]
25		1) GP B 2) GP C1, 9 eq. DIPEA	30	yellow solid	0.66 (CH_2Cl_2/MeOH 9:1)	191 - 195	622.9 $[M+H]^+$	24.3 Method A
26		1) GP B 2) GP C1, 9 eq. DIPEA	21	white solid	0.34 (petrol ether / ethyl acetate 1:1)	204 - 205	598.9 $[M+H]^+$	25.5 Method B
27		1) GP B, 3 eq. Thiohpenole added 2) GP C1, 9 eq. DIPEA	2	white solid	0.16 (CH_2Cl_2/MeOH/AcOH 9.5:0.5:0.1)	255 - 257	541.2 $[M+H]^+$	21.4 Method A
28		1) GP B 2) GP C1, 9 eq. DIPEA	99	pale brown solid	0.80 (CH_2Cl_2/MeOH/AcOH 9:1:0.1)	90 - 95	590.0 $[M+H]^+$	25.0 Method B
29		1) GP B 2) GP C1, 9 eq. DIPEA	1.6	pale yellow oil	0.68 (CH_2Cl_2/MeOH 9:0.5)	n.d.	585.2 $[M+H]^+$	n.d.

Example No.	Structure	Procedure	Yield [%]	Product	R_f	M.p. [°C]	ESI-MS	HPLC t_R[min]
30		1) GP B 2) GP C1, 9 eq. DIPEA	73	pale brown solid	0.66 (CH_2Cl_2/MeOH 9:1)	186 - 189	627.4 $[M+H]^+$	26.2 Method A
31		GP C2	–	–	–	n.d.	–	n.d.
32		GP C2	–	–	–	n.d.	–	n.d.
33		1) GP B 2) GP C1, 9 eq. DIPEA	16	yellow solid	0.90 (CH_2Cl_2/MeOH 9:1)	125 - 130	580.2 $[M+H]^+$	24.2 Method A
34		GP C2	–	–	–	n.d.	–	n.d.

Example No.	Structure	Procedure	Yield [%]	Product	R_f	M.p. [°C]	ESI-MS	HPLC t_R[min]
35		1) GP B 2) GP C1, 9 eq. DIPEA	97	pale brown solid	0.62 (CH_2Cl_2/MeOH/AcOH 9:1:0.1)	188 - 189	756.4 $[M+H]^+$	n.d.
36		1) GP B 2) GP C1, 3 eq. DIPEA	64	white solid	0.50 (CH_2Cl_2/MeOH 9:1)	197 - 198	547.0 $[M+H]^+$	21.8 Method A
37		GP C2, 3 eq. DIPEA	82	white solid	0.80 (CH_2Cl_2/MeOH 9:1)	188 - 189	613.3 $[M+H]^+$	n.d.
38		GP C2	–	–	–	n.d.	–	n.d.

Step D

General procedure D1 (GP D1): ester saponification

A solution or suspension of the ester and 1.1 eq. KOH in water/ethanol, methanol and/or dioxane was stirred at 25–50°C for 2–24 h. After washing with methyl-tert-butylether (80 ml) the volume of the reaction mixture was reduced until a slight turbidity was observed. The solution was acidified to pH 2 by the addition of 1 N aqueous HCl. The precipitate was collected by filtration, washed with cold water and dried in vacuum.

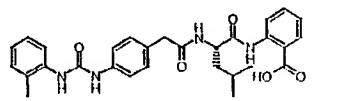
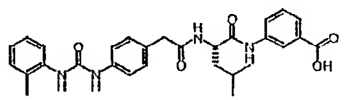
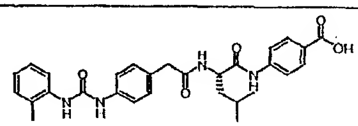
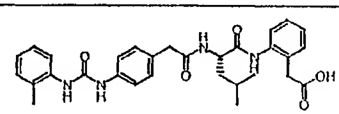
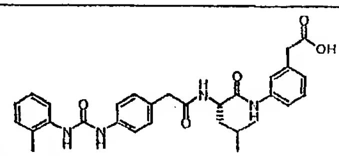
General procedure D2 (GP D2): deprotection of benzyl esters / benzyl carbamates

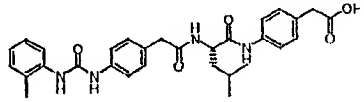
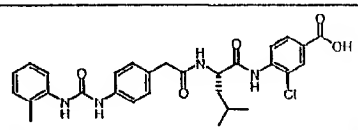
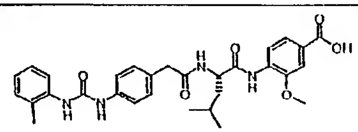
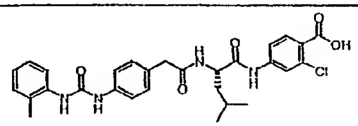
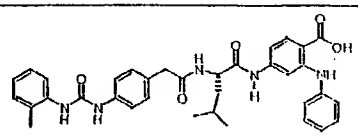
A solution or suspension of the ester and 10% Pd-C (10%) in dimethylformamide was hydrogenated for 12 h at r.t. and 50 bar hydrogen pressure. The reaction mixture was filtered through celite. Evaporation of the filtrate and purification of the crude product by preparative HPLC (LiChrospher RP-18, 12 µM, 250x25 mm; flow rate 40 ml/min; eluent: acetonitrile/water mixture with 0.1% trifluoroacetic acid (vol./vol.), linear gradient of: 0 min. = 40% acetonitrile, 20 min. = 80% acetonitrile) afforded the product.

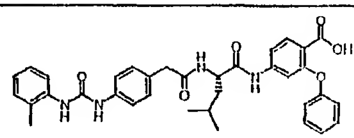
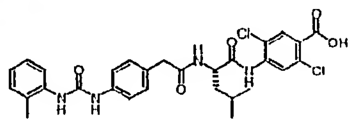
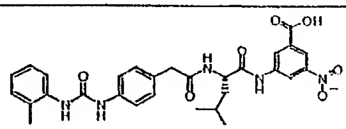
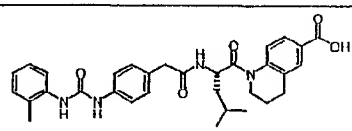
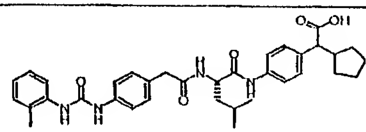
General procedure D3 (GP D3): deprotection of benzyl esters

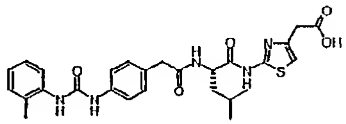
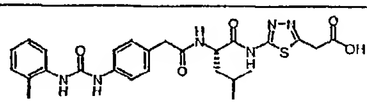
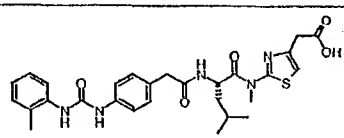
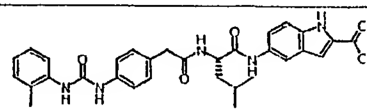
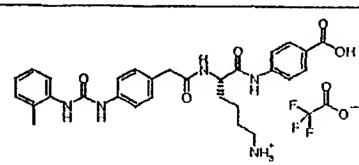
A solution or suspension of the ester and 10% Pd-C (10%) in tetrahydrofurane was hydrogenated for 18 h at r.t. under atmospheric hydrogen pressure. The reaction mixture was filtered through celite. Evaporation of the filtrate afforded the product.

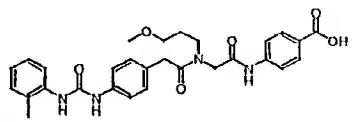
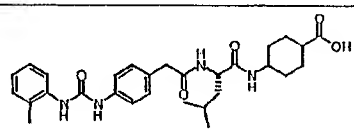
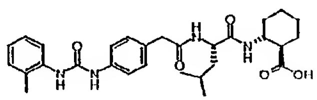
Table 3: following examples were prepared according to the general procedures D1 – D3:

Example No.	Structure	Procedure	Yield [%]	Product	R_f	M.p. [°C]	ESI-MS	HPLC t_R[min]
39		GP D1; 10 eq. KOH	–	–	–	190	–	n.d.
40		GP D1; 10 eq. KOH	–	–	–	220	–	n.d.
41		GP D1; 10 eq. KOH	90	white solid	0.24 (CH_2Cl_2/MeOH/AcOH 9:1:0.1)	219-223	517.0 $[M+H]^+$	21.3 Method A
42		GP D1; 10 eq. KOH	87	yellow solid	0.06 (CH_2Cl_2/MeOH/AcOH 9:1:0.1))	186-190	531 $[M+H]^+$	26.6 Method A
43		GP D1; 10 eq. KOH	83	white solid	0.06 (CH_2Cl_2/MeOH/AcOH 9:1:0.1)	178-181	531 $[M+H]^+$	26.8 Method A

Example No.	Structure	Procedure	Yield [%]	Product	R_f	M.p. [°C]	ESI-MS	HPLC t_R[min]
44		GP D1; 10 eq. KOH	–	–	–	206	–	n.d.
45		GP D1; 1.5 eq. KOH	64	pale brown solid	0.34 (CH_2Cl_2/MeOH/AcOH 9:1:0.1)	154-158	551.3 $[M+H]^+$	22.2 Method B
46		GP D1; 1.6 eq. NaOH	16	white solid	0.28 (CH_2Cl_2/MeOH/AcOH 9:1:0.1)	138-142	546.8 $[M+H]^+$	23.1 Method B
47		GP D1; 1.1 eq. KOH	36	pale red solid	0.36 (CH_2Cl_2/MeOH/AcOH 9:1:0.1)	178 -180	551.1 $[M+H]^+$	21.6 Method A
48		GP D1; 3.5 eq. KOH	68	pale brown solid	0.30 (CH_2Cl_2/MeOH/AcOH 9:1:0.1)	164-169	608.0 $[M+H]^+$	23.7 Method A

Example No.	Structure	Procedure	Yield [%]	Product	R_f	M.p. [°C]	ESI-MS	HPLC t_R[min]
49		GP D1; 1.1 eq. KOH	18	pale brown solid	0.62 (CH_2Cl_2/MeOH/AcOH 9:1:0.1)	158-160	609.2 $[M+H]^+$	23.1 Method A
50		GP D1; 1.1 eq. KOH	8	pale red solid	0.68 (CH_2Cl_2/MeOH/AcOH 9:1:0.1)	185-188	584.9 $[M+H]^+$	22.5 Method A
51		GP D1; 1.5 eq. NaOH	45	yellow solid	0.10 (CH_2Cl_2/MeOH 9:1)	188-190	562.0 $[M+H]^+$	23.5 Method A
52		GP D1; 1.1 eq. KOH	76	white foam	n.d.	n.d.	557 $[M+H]^+$ HPLC-MS	22.8 Method A
53		GP D1; 1.1 eq. KOH	26	white solid	0.74 (CH_2Cl_2/MeOH/AcOH 9:1:0.1)	206-208	599.4 $[M+H]^+$	19.2 23.5 Method B; 2 dia-steromeres

Example No.	Structure	Procedure	Yield [%]	Product	R_f	M.p. [°C]	ESI-MS	HPLC t_R[min]
54		GP D1; 1.5 eq. KOH	26	pale brown solid	0.30 (CH_2Cl_2/MeOH/AcOH 9:1:0.1)	178-180	538.2 $[M+H]^+$	29.4 Method A
55		GP D1; 1.5 eq. KOH	33	pale brown solid	0.18 (CH_2Cl_2/MeOH/AcOH 9:1:0.1)	187-189	539.2 $[M+H]^+$	28.7 Method A
56		GP D1; 1.1 eq. KOH	2	pale brown solid	0.26 (CH_2Cl_2/MeOH/AcOH 9:1:0.1)	172 - 174	552.07 $[M+H]^+$	21.3 Method A
57		GP D1; 1.5 eq. KOH	22	pale brown solid	0.08 (CH_2Cl_2/MeOH/AcOH 9:1:0.1)	240 decomposition	556.2 $[M+H]^+$	29.4 Method A
58		GP D2	3	white solid	0.05 (CH_2Cl_2/MeOH/AcOH 9:1:0.1)	168-169	532.1 $[M+H]^+$ LC-MS	n.d.

Example No.	Structure	Procedure	Yield [%]	Product	R_f	M.p. [°C]	ESI-MS	HPLC t_R[min]
59		GP D1; 1.1 eq. KOH	76	white solid	0.48 (CH_2Cl_2/MeOH/AcOH 9:1:0.1)	210-218	570.8 $[M+K]^+$	20.0 Method A
60		GP D3	95	white solid	0.12 (CH_2Cl_2/MeOH/AcOH 9.5:0.5:0.1)	175 decomposition	523.2 $[M+H]^+$	20.2 Method B
61		GP D1, 1.5 eq. KOH	1	pale brown solid	0.10 (CH_2Cl_2/MeOH/AcOH 9.5:0.5:0.1)	n.d.	523.2 $[M+H]^+$	20.0 Method A

In vitro assay: adhesion of Jurkat/Ramos cells to immobilized VCAM-1 (domains 1-3)

Preparation of VCAM-1 (extracellular domains 1-3)

Complementary DNA (cDNA) encoding 7-domain form of VCAM-1 (GenBank accession #M60335) was obtained using Rapid-ScreenTM cDNA library panels (OriGene Technologies, Inc) at Takara Gene Analysis Center (Shiga, Japan). The primers used were 5'-CCA AGG CAG AGT ACG CAA AC-3' (sense) and 5'-TGG CAG GTA TTA TTA AGG AG-3' (antisense). PCR amplification of the 3-domain VCAM-1 cDNA was perform using *Pfu* DNA polymerase (Stratagene) with the following sets of primers: (U-VCAMd1-3) 5'-CCA TAT GGT ACC TGA TCA ATT TAA AAT CGA GAC CAC CCC AGA A-3'; (L-VCAMd1-3) 5'-CCA TAT AGC AAT CCT AGG TCC AGG GGA GAT CTC AAC AGT AAA-3'. PCR cycle was 94 °C for 45 sec, 55 °C for 45 sec, 72 °C for 2 min, repeating 15 cycles. After the purification of the PCR product, the fragment was digested with KpnI-AvrII. The digested fragment was ligated into pBluescript IISK(-) (Strategene), which was linearized by digesting with KpnI-XhoI. The ligation was followed by transformation to a Dam/Dcm methylase-free E. coli strain SCS110 (Strategene) to create the donor plasmid pHH7. To direct VCAM-1 molecule into the insect cell secretory pathway, the VCAM-1 coding sequence was fused to signal peptide sequence of honeybee melittin. The resulting melittin-VCAM fusion was placed in correct orientation to the baculovirus polyhedrin promoter. Baculovirus transfer vector containing first 3-domain form VCAM-1 (pH10) was constructed by ligation of 0.9 kb fragment from AvrII/Klenow/BclI digests of pH7 into SalI/Klenow/BamHI digests of pMelBacB (Invitrogen). Recombinant baculovirus was generated by using Bac-N-Blue™ Transfection kit (Invitrogen) according to the manufacture's instruction. The recombinant virus was amplified by infection to High-Five™ insect cells for 5 – 6 days, and virus titer was determined by plaque assay.

High-Five^{TM} insect cells were pelleted in a 225 ml conical tube by centrifugation at 1000 rpm for 5 min. After discarding the supernatant, the pellet was resuspended in 1.5 x 10^9 pfu (MOI = 5) of high-titer virus solution, followed by incubation for 1.5 hours at room temperature. The cells were pelleted again and washed once in fresh Express Five^{TM} serum free medium. The cells were pelleted again and finally, resuspended in 200 ml of fresh Express Five TM medium, transferred to a 1,000 ml shaker flask, and incubated in a shaker at 27 °C, 130 rpm, for 48 hours before the culture supernatant was collected. The purification of 3-domain form of VCAM-1 from the culture supernatant was performed by one-step anion exchange chromatography. Protein concentration was determined by using Coomassie protein assay reagent (Pierce) according to the manufacture's instruction.

Preparation of VCAM-1 coated microtiter plates

Recombinant human VCAM-1 (extracellular domains 1-3) was dissolved at 1.0 µg/ml in PBS. Each well of the microtiter plates (Nalge Nunc International, Fluoronunc Cert, 437958) was coated with 100 µl of substrate or for background control with buffer alone for 15 hours at 4 C. After discarding the substrate solution, the wells were blocked using 150 µl per well of block solution (Kirkegaard Perry Laboratories, 50-61-01) for 90 minutes. The plate was washed with wash buffer containing 24 mM Tris-HCl (pH 7.4), 137 mM NaCl, 27 mM KCl and 2 mM $MnCl_2$ just before addition of the assay.

In vitro assay using Jurkat cells

Preparation of fluorescence labeled Jurkat cells:

Jurkat cells (American Type Culture Collection, Clone E6-1, ATCC TIB-152) were cultured in RPMI 1640 medium (Nikken Bio Medical Laboratory, CM1101) supplemented with 10% fetal bovine serum (Hyclone, A-1119-L), 100 U/ml penicilin (Gibco BRL, 15140-122) and 100 µg/ml streptomycin (Gibco BRL, 15140-122) in a humidified incubator at 37 °C with 5% CO_2.

Jurkat cells were incubated with phosphate balanced solution (PBS, Nissui, 05913) containing 25 μM of 5(-and –6)-carboxyfluorescein diacetate, succinimidyle ester (CFSE, Dojindo Laboratories, 345-06441) for 20 min at room temperature while gently swirling every 5 min. After centrifugation at 1000 rpm for 5 min, the cell pellet was resuspended with adhesion assay buffer at a cell density of 4×10^6 cells/ml. The adhesion assay buffer was composed of 24 mM Tris-HCl (pH 7.4), 137 mM NaCl, 27 mM KCl, 4 mM glucose, 0.1 % bovine serum albumin (BSA, Sigma, A9647) and 2 mM $MnCl_2$.

Assay **procedure (Jurkat cells)**

The assay solution containing each test compounds was transferred to the VCAM-1 coated plates. The final concentration of each test compounds was 5 μM, 10 μM or various concentrations ranging from 0.0001 μM to 10 μM using a standard 5-point serial dilution. The assay solution containing the labeled Jurkat cells was transferred to the VCAM-1 coated plates at a cell density of 2×10^5 cells per well and incubated for 1 hour at 37 C. The non-adherent cells were removed by washing the plates 3 times with wash buffer. The adherent cells were broken by addition of 1 % Triton X-100 (Nacalai Tesque, 355-01). Released CFSC was quantified fluorescence measurement in a fluorometer (Wallac, ARVO 1420 multilabel counter).

The adhesion of Jurkat cells to VCAM-1 was analyzed by percent binding calculated by the formula:

100 x (FTS – FBG) / (FTB – FBG) = % binding, where FTB is the total fluorescent intensity from VCAM-1 coated wells without test compound; FBG is the fluorescent intensity from wells lacking VCAM-1 and FTS is the fluorescent intensity from wells containing the test compound of this invention.

In Vitro Assay using Ramos cells

Preparation of fluorescence labeled Ramos cells:

Ramos cells (American Type Culture Collection, Clone CRL-1596) were cultured in RPMI 1640 medium (Nikken Bio Medical Laboratory, CM1101) supplemented with 10% fetal bovine serum (Hyclone, A-1119-L), 100 U/ml penicilin (Gibco BRL, 15140-122) and 100 μg/ml streptomycin (Gibco BRL, 15140-122) in a humidified incubator at 37 °C with 5% CO_2.

Ramos cells were incubated with phosphate balanced solution (PBS, Nissui, 05913) containing 25 μM of 5(-and –6)-carboxyfluorescein diacetate, succinimidyle ester (CFSE, Dojindo Laboratories, 345-06441) for 20 min at room temperature while gently swirling every 5 min. After centrifugation at 1000 rpm for 5 min, the cell pellet was resuspended with adhesion assay buffer at a cell density of 4×10^6 cells/ml. The adhesion assay buffer was composed of 24 mM Tris-HCl (pH 7.4), 137 mM NaCl, 27 mM KCl, 4 mM glucose, 0.1 % bovine serum albumin (BSA, Sigma, A9647) and 2 mM $MnCl_2$.

Assay procedure (Ramos cells)

The assay solution containing each test compounds or 5 μg/ml anti-CD49d monoclonal antibody (Immunotech, 0764) was transferred to the VCAM-1 coated plates. The final concentration of each test compounds was 5 μM, 10 μM or various concentrations ranging from 0.0001 μM to 10 μM using a standard 5-point serial dilution. The assay solution containing the labeled Ramos cells was transferred to the VCAM-1 coated plates at a cell density of 2×10^5 cells per well and incubated for 1 hour at 37 C. The non-adherent cells were removed by washing the plates 3 times with wash buffer. The adherent cells were broken by addition of 1 % Triton X-100 (Nacalai Tesque, 355-01). Released CFSC was quantified fluorescence measurement in a fluorometer (Wallac, ARVO 1420 multilabel counter).

The adhesion of Ramos cells to VCAM-1 was analyzed by percent binding calculated by the formula:

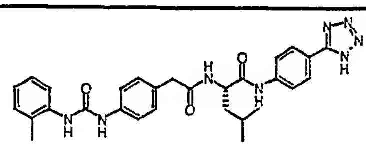
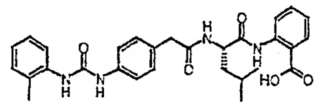
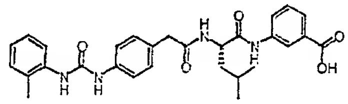
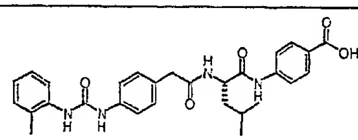
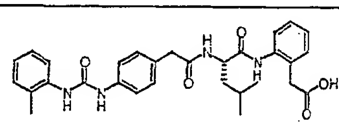
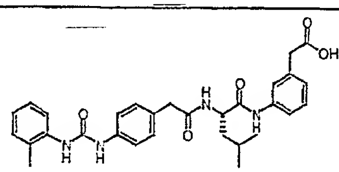
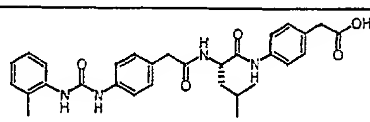
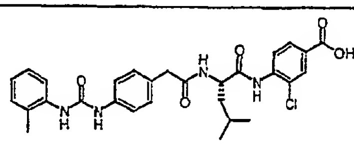
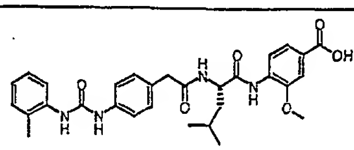
100 x (FTS – FBG) / (FTB – FBG) = % binding, where FTB is the total fluorescent intensity from VCAM-1 coated wells without test compound; FBG is the fluorescent intensity from wells with anti-CD49d monoclonal antibody and FTS is the fluorescent intensity from wells containing the test compound of this invention.

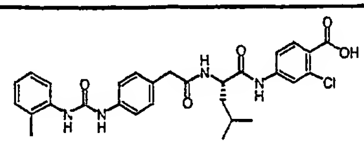
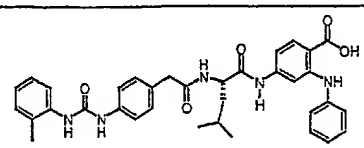
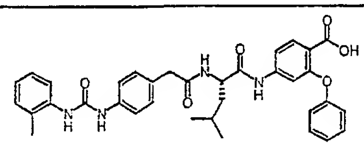
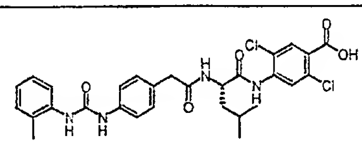
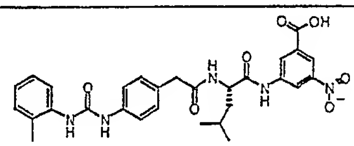
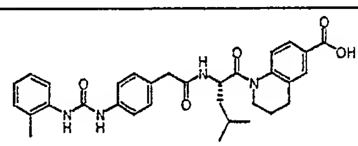
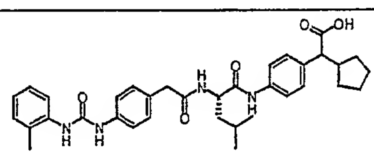
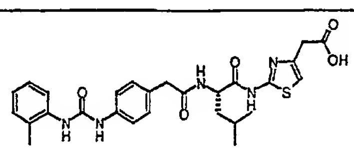
In vitro activity:

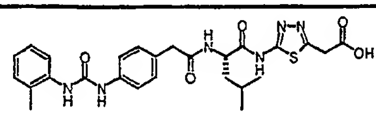
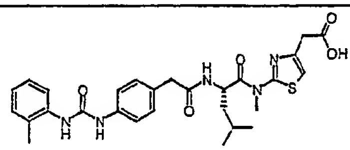
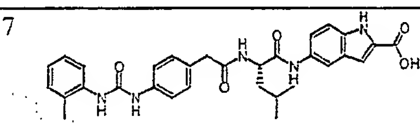
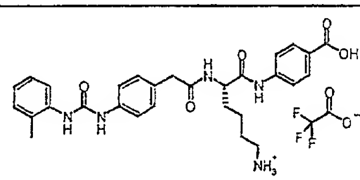
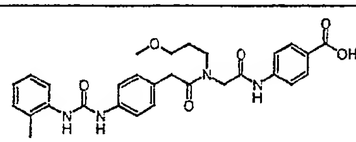
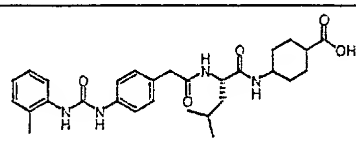
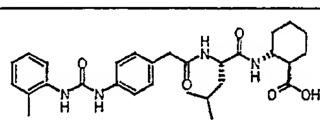
In the Jurkat – VCAM-1 assay (indicated as Jurkat – VCAM-1) and the Ramos – VCAM-1 (indicated as Ramos – VCAM-1) the observed IC_{50} value ranges are indicated Table 4.

$D > 10\ \mu M \geq C > 2\ \mu M \geq B > 0.5\ \mu M \geq A$

Table 4.

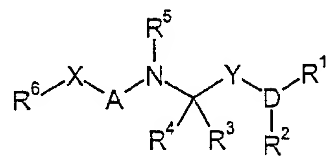
No.	Structure	IC_{50}	Cell Type
27		C	Ramos
39		D	Jurkat
40		D	Jurkat
41		A	Jurkat
42		D	Jurkat
43		B	Jurkat
44		C	Jurkat
45		A–B	Jurkat
46		D	Ramos

No.	Structure	IC_{50}	Cell Type
47		A	Ramos
48		A	Ramos
49		A	Ramos
50		C	Ramos
51		C	Ramos
52		C	Ramos
53		C	Jurkat
54		C	Jurkat

No	Structure	IC_{50}	Cell Type
55		C	Jurkat
56		D	Ramos
57		D	Jurkat
58		A	Ramos
59		A	Ramos
60		C	Jurkat
61		C	Ramos

Claims:

1. Compounds of the general formula (I),



(I)

wherein

R^1 represents a 4- to 9-membered saturated, unsaturated or aromatic cyclic residue,

which can contain 0 to 3 heteroatoms selected independently from the group N, S and O,

wherein the cyclic residue R^1 can be annulated with a 4- to 8-membered saturated, unsaturated or aromatic cyclic residue, which can contain 0 to 2 heteroatoms selected independently from the group N, S and O,

and wherein the cyclic residue R^1 and/or a ring annulated to the cyclic residue R^1 is substituted by 1 to 2 substituents $-R^{1-1}-R^{1-2}-R^{1-3}-Z$, wherein

R^{1-1} represents a bond, -O-, -S-, NR^{1-4}, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_6 or C_{10} aryl, C_3-C_7 cycloalkyl or a 4-9-membered saturated or unsaturated heterocyclic residue containing up to 3 heteroatoms selected from the group oxygen, nitrogen or sulfur,

wherein R^{1-1} can optionally be substituted by 1 to 2 substituents selected from the group R^{1-5},

wherein R^{1-5} represents hydrogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_6 or C_{10} aryl, C_3-C_7 cycloalkyl or a 4-9-membered saturated or unsaturated heterocyclic residue containing up to 3 heteroatoms selected from the group oxygen, nitrogen or sulfur,

wherein R^{1-5} can optionally be substituted by 1 to 3 substituents selected from the group C_1-C_4 alkyl, C_1-C_4 alkyloxy, phenyl, C_3-C_6 cycloalkyl, halogen, nitro, cyano, oxo,

R^{1-2} represents a bond, -O-, -S-, NR^{1-4}, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl,

wherein R^{1-2} can optionally be substituted by C_1-C_{10} alkyl, C_2-C_{10} alkenyl, $C_2 - C_{10}$ alkynyl or R^{1-6},

wherein R^{1-6} represents hydrogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_6 or C_{10} aryl, C_3-C_7 cycloalkyl or a 4-9-membered saturated or unsaturated heterocyclic residue containing up to 3 heteroatoms selected from the group oxygen, nitrogen or sulfur,

wherein R^{1-6} can optionally be substituted by 1 to 3 substituents selected from the group C_1-C_4 alkyl, C_1-C_4 alkyloxy, phenyl, C_3-C_6 cycloalkyl, halogen, nitro, cyano, oxo,

R^{1-4} can optionally be hydrogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl or C_2-C_{10} alkynyl,

R^{1-3} represents a bond, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl,

wherein R^{1-3} can optionally be substituted by C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl or R^{1-7},

wherein R^{1-7} represents hydrogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_6 or C_{10} aryl, C_3-C_7 cycloalkyl or a 4-9-membered saturated or unsaturated heterocyclic residue containing up to 3 heteroatoms selected from the group oxygen, nitrogen or sulfur,

wherein R^{1-7} can optionally be substituted by 1 to 3 substituents selected from the group C_1-C_4 alkyl, C_1-C_4 alkyloxy, phenyl, C_3-C_6 cycloalkyl, halogen, nitro, cyano, oxo,

with the proviso that, where R^{1-3} is a bond, R^{1-2} is not a heteroatom,

and with the proviso that R^{1-1} and R^{1-2} are not both heteroatom at the same time,

Z represents $-C(O)OR^{Z-1}$, $-C(O)NR^{Z-2}R^{Z-3}$, $-SO_2NR^{Z-2}R^{Z-3}$, $-SO(OR^{Z-1})$, $-SO_2(OR^{Z-1})$, $-P(O)R^{Z-1}(OR^{Z-3})$, $-PO(OR^{Z-1})(OR^{Z-3})$ or 5-tetrazolyl,

wherein R^{Z-2} is hydrogen, C_1-C_4 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6 or C_{10} aryl, $-C(O)R^{Z-4}$ or $-SO_2R^{Z-4}$,

wherein R^{Z-4} is C_1-C_4 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6 or C_{10} aryl,

wherein R^{Z-4} can optionally be substituted by 1 to 3 substituents selected from the group halogen, nitro, cyano, oxo,

R^{Z-1} and R^{Z-3} are identical or different and represent hydrogen, C_1-C_4 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6 or C_{10} aryl or benzyl,

wherein R^{Z-1} and R^{Z-3} can optionally be substituted by 1 to 3 substituents selected from the group C_1-C_4 alkyl, C_1-C_4 alkyloxy, halogen, nitro, cyano,

the cyclic residue R^1 and/or a ring annulated to the cyclic residue formed by R^1 can optionally be substituted by 0 to 2 substituents R^{1-8}, halogen, nitro, amino, cyano and oxo,

wherein

R^{1-8} can independently be selected from the group of C_1-C_4 alkyl, C_1-C_4 alkyloxy, phenyl, phenoxy, phenylamino, C_3-C_6 cycloalkyl, and

R^2 represents hydrogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_6 or C_{10} aryl, C_3-C_7 cycloalkyl or a 4-9-membered saturated or unsaturated heterocyclic residue containing up to 2 heteroatoms selected from the group oxygen, nitrogen or sulfur,

which can optionally be substituted by 1 to 3 radicals R^{2-1},

wherein R^{2-1} represents C_{1-4} alkyl, trifluormethyl, trifluormethoxy, $-OR^{2-2}$, $-SR^{2-2}$, $NR^{2-3}R^{2-4}$, $-C(O)R^{2-2}$, $S(O)R^{2-2}$, $-SO_2R^{2-2}$, $-CO_2R^{2-2}$, $-OC(O)R^{2-2}$, $-C(O)NR^{2-3}R^{2-4}$, $-NR^{2-2}C(O)R^{2-3}$, $-SO_2NR^{2-3}R^{2-4}$, $NR^{2-2}SO_2R^{2-3}$, $-NR^{2-2}C(O)NR^{2-3}R^{2-4}$, $-NR^{2-2}C(O)OR^{2-3}$, $-OC(O)NR^{2-3}R^{2-4}$, halogen, cyano, nitro or oxo,

wherein R^{2-2} represents hydrogen, C_1-C_4 alkyl, C_3 – C_6 cycloalkyl, C_6 or C_{10} aryl

which can optionally be substituted by 1 substituent selected from the group C_1-C_4 alkyl, C_1-C_4 alkyloxy, phenyl, C_3-C_6 cycloalkyl, halogen, nitro, cyano,

and wherein R^{2-3} and R^{2-4} are identical or different and represent hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_6 or C_{10} aryl,

or

R^{2-3} and R^{2-4} together form a 4-7-membered ring, which includes the nitrogen atom to which R^{2-3} and R^{2-4} are bonded and which contains up to 2 additional heteroatoms selected from the group oxygen, nitrogen or sulfur and which contains up to 2 double bonds,

and if R^2 is alkyl, R^2 together with the cyclic residue R^1 and D can form a ring,

R^3 represents hydrogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_6 or C_{10} aryl, C_3-C_7 cycloalkyl or a 4-9-membered saturated or unsaturated heterocyclic residue containing up to 2 heteroatoms selected from the group oxygen, nitrogen or sulfur,

wherein R^3 can optionally be substituted by 1 to 3 radicals R^{3-1},

and wherein R^3 can furthermore be single-foldedly substituted by C_3-C_7 cycloalkyl, C_6 or C_{10} aryl, C_4-C_9 heteroaryl or a heterocyclic residue containing up to 2 heteroatoms selected from the group oxygen, nitrogen or sulfur,

which can be annulated with a phenyl ring,

and which can optionally be substituted by 1 to 3 radicals R^{3-1},

wherein R^{3-1} represents C_1-C_4 alkyl, trifluormethyl, trifluormethoxy, $-OR^{3-2}$, $-SR^{3-2}$, $NR^{3-3}R^{3-4}$, $-C(O)R^{3-2}$, $S(O)R^{3-2}$, $-SO_2R^{3-2}$, $-OC(O)R^{3-2}$, $-C(O)NR^{3-3}R^{3-4}$, $-NR^{3-2}C(O)R^{3-3}$, $-SO_2NR^{3-3}R^{3-4}$, $NR^{3-2}SO_2R^{3-3}$, $-NR^{3-2}C(O)NR^{3-3}R^{3-4}$, $-NR^{3-2}C(O)OR^{3-3}$, $-OC(O)NR^{3-3}R^{3-4}$, $-CO_2R^{3-5}$, halogen, cyano, nitro or oxo,

wherein R^{3-2} represents hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_6 or C_{10} aryl

which can optionally be substituted by 1 substituent selected from the group C_1-C_4 alkyl, C_1-C_4 alkyloxy, phenyl, C_3-C_6 cycloalkyl, halogen, nitro, cyano,

and wherein R^{3-3} and R^{3-4} are identical or different and represent hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_6 or C_{10} aryl, benzyl or 9-fluorenylmethyl,

or

R^{3-3} and R^{3-4} together form a 4-7-membered ring, which includes the nitrogen atom to which R^{3-3} and R^{3-4} are bonded and which contains up to 2 additional heteroatoms selected from the group oxygen, nitrogen or sulfur and which contains up to 2 double bonds,

and wherein R^{3-5} represents hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_6 or C_{10} aryl

R^4 represents hydrogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_6 or C_{10} aryl, C_3-C_7 cycloalkyl or a 4-9-membered saturated or unsaturated heterocyclic residue containing up to 2 heteroatoms selected from the group oxygen, nitrogen or sulfur,

which can optionally be substituted by 1 to 3 radicals R^{4-1},

and which can furthermore be single-foldedly substituted by C_3-C_7 cycloalkyl, C_6 or C_{10} aryl, C_4-C_9 heteroaryl or a heterocyclic residue containing up to 2 heteroatoms selected from the group oxygen, nitrogen or sulfur,

which can optionally be substituted by 1 to 3 radicals R^{4-1},

wherein R^{4-1} represents $C_1 - C_4$ alkyl, trifluormethyl, trifluormethoxy, $-OR^{4-2}$, $-SR^{4-2}$, $NR^{4-3}R^{4-4}$, $-C(O)R^{4-2}$, $S(O)R^{4-2}$, $-SO_2R^{4-2}$, $-OC(O)R^{4-2}$, $-C(O)NR^{4-3}R^{4-4}$, $-NR^{4-2}C(O)R^{4-3}$, $-SO_2NR^{4-3}R^{4-4}$, $NR^{4-2}SO_2R^{4-3}$, $-NR^{4-2}C(O)NR^{4-3}R^{4-4}$, $-NR^{4-2}C(O)OR^{4-3}$, $-OC(O)NR^{4-3}R^{4-4}$, $-CO_2R^{4-5}$, halogen, cyano, nitro or oxo,

wherein R^{4-2} represents hydrogen, $C_1 - C_4$ alkyl, $C_3 - C_6$ cycloalkyl, C_6 or C_{10} aryl

which can optionally be substituted by 1 substituent selected from the group C_1-C_4 alkyl, C_1-C_4 alkyloxy, phenyl, C_3-C_6 cycloalkyl, halogen, nitro, cyano,

and wherein R^{4-3} and R^{4-4} are identical or different and represent hydrogen, C_{1-4} alkyl, C_3-C_6 cycloalkyl, C_6 or C_{10} aryl,

or

R^{4-3} and R^{4-4} together form a 4-7-membered ring, which includes the nitrogen atom to which R^{4-3} and R^{4-4} are bonded and which contains up to 2 additional heteroatoms selected from the group oxygen, nitrogen or sulfur and which contains up to 2 double bonds,

and wherein R^{4-5} represents hydrogen, $C_1 - C_4$ alkyl, $C_3 - C_6$ cycloalkyl, C_6 or C_{10} aryl

R^5 represents hydrogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_6 or C_{10} aryl, C_3-C_7 cycloalkyl or a 4-9-membered saturated or unsaturated heterocyclic residue containing up to 2 heteroatoms selected from the group oxygen, nitrogen or sulfur,

which can optionally be substituted by 1 to 3 radicals R^{5-1},

and which can furthermore be single-foldedly substituted by C_3-C_7 cycloalkyl, C_6 or C_{10} aryl, C_4-C_9 heteroaryl or a saturated or unsaturated heterocyclic residue containing up to 2 heteroatoms selected from the group oxygen, nitrogen or sulfur,

which can optionally be substituted by 1 to 3 radicals R^{5-1},

wherein R^{5-1} represents C_1-C_4 alkyl, phenyl, trifluormethyl, trifluormethoxy, -OR^{5-2}, -SR^{5-2}, $NR^{5-3}R^{5-4}$, -$C(O)R^{5-2}$, $S(O)R^{5-2}$, -SO_2R^{5-2}, -CO_2R^{5-2}, -$OC(O)R^{5-2}$, -$C(O)NR^{5-3}R^{5-4}$, -$NR^{5-2}C(O)R^{5-3}$, -$SO_2NR^{5-3}R^{5-4}$, $NR^{5-2}SO_2R^{5-3}$, -$NR^{5-2}C(O)NR^{5-3}R^{5-4}$, -$NR^{5-2}C(O)OR^{5-3}$, -$OC(O)NR^{5-3}R^{5-4}$, halogen, cyano, nitro or oxo,

wherein R^{5-2} represents hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_6 or C_{10} aryl

which can optionally be substituted by 1 substituent selected from the group C_1-C_4 alkyl, C_1-C_4 alkyloxy, phenyl, C_3-C_6 cycloalkyl, halogen, nitro, cyano,

and wherein R^{5-3} and R^{5-4} are identical or different and represent hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_6 or C_{10} aryl,

or

R^{5-3} and R^{5-4} together form a 4-7-membered ring, which includes the nitrogen atom to which R^{5-3} and R^{5-4} are bonded and which contains up to 2 additional heteroatoms selected from the group oxygen, nitrogen or sulfur and which contains up to 2 double bonds,

R^6 represents phenyl or a 5- to 6-membered aromatic heterocyclic residue containing up to 3 heteroatoms independently selected from the group oxygen, nitrogen or sulfur,

which can optionally be annulated with a 5- to 8-membered saturated or unsaturated cyclic residue containing up to 2 heteroatoms independently selected from the group oxygen, nitrogen or sulfur,

and which can optionally be independently substituted by 1 to 3 radicals R^{6-1} and which can furthermore be single-foldedly substituted by C_3-C_7 cycloalkyl, C_6 or C_{10} aryl, C_4-C_9 heteroaryl or a heterocyclic residue containing up to 2 heteroatoms selected from the group oxygen, nitrogen or sulfur,

wherein the latter cyclic substituents can themselves optionally be substituted by 1 to 3 radicals R^{6-1},

wherein R^{6-1} represents C_1-C_4 alkyl, trifluormethyl, trifluormethoxy, $-OR^{6-4}$, $-SR^{6-2}$, $NR^{6-3}R^{6-4}$, $-C(O)R^{6-2}$, $S(O)R^{6-2}$, $-SO_2R^{6-2}$, $-CO_2R^{6-2}$, $-OC(O)R^{6-2}$, $-C(O)NR^{6-3}R^{6-4}$, $-NR^{6-2}C(O)R^{6-2}$, $-SO_2NR^{6-3}R^{6-4}$, $-NR^{6-2}SO_2R^{6-2}$, $-NR^{6-2}C(O)NR^{6-3}R^{6-4}$, $-NR^{6-2}C(S)NR^{6-3}R^{6-4}$, $-NR^{6-2}C(O)OR^{6-4}$, $-OC(O)NR^{6-3}R^{6-4}$, halogen, cyano, nitro or oxo,

wherein R^{6-2} represents hydrogen, C_1-C_4 alkyl, $C_3 - C_6$ cycloalkyl, C_6 or C_{10} aryl

which can optionally be substituted by 1 to 3 substituents selected from the group C_1-C_4 alkyl, C_1-C_4 alkyloxy, phenyl, C_3-C_6 cycloalkyl, halogen, nitro, cyano,

and wherein R^{6-3} and R^{6-4} are identical or different and represent hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_6 or C_{10} aryl or a 4-9-membered saturated or unsaturated heterocyclic residue containing up to 2 heteroatoms selected from the group oxygen, nitrogen or sulfur,

which can optionally be substituted by 1 to 2 substituents selected from the group C_1-C_4 alkyl, phenyl, C_3-C_7 cycloalkyl, C_1-C_4 alkyloxy, halogen, nitro, cyano,

or

R^{6-3} and R^{6-4} together form a 4-7-membered ring, which includes the nitrogen atom to which R^{6-3} and R^{6-4} are bonded and which contains up to 2 additional heteroatoms selected from the group oxygen, nitrogen or sulfur and which contains up to 2 double bonds, which can optionally be substituted by 1 to 2 substituents selected from the group C_1-C_4 alkyl, phenyl, benzyl, C_3-C_7 cycloalkyl, C_1-C_4 alkyloxy, halogen, nitro, cyano, oxo,

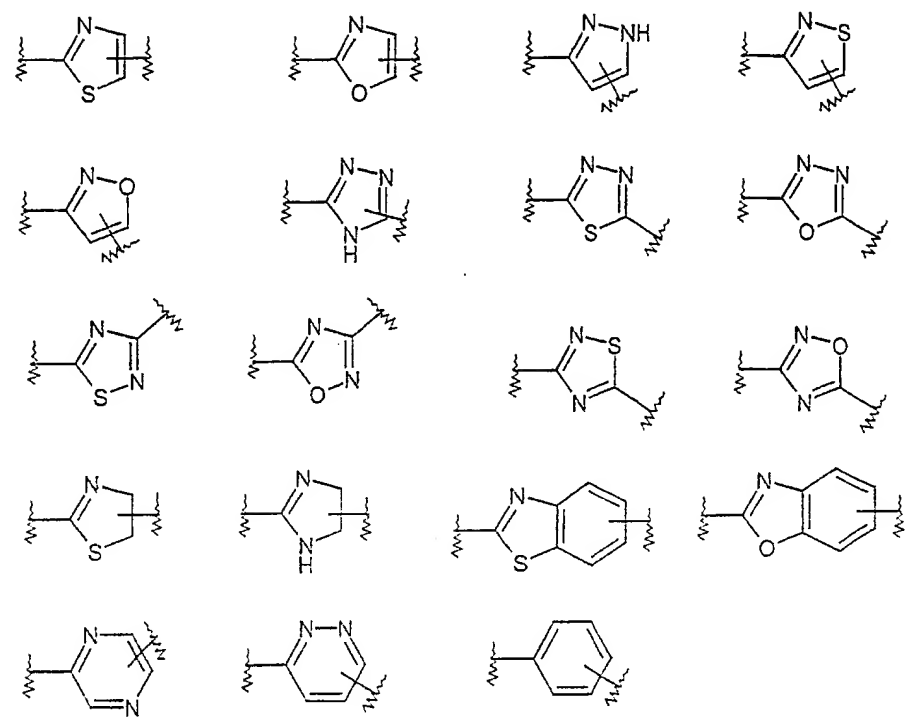
and in case that R^1 represents a 3-amino benzoic acid derivative and R^{6-1} represents -OR^{6-4}, -$C(O)NR^{6-3}R^{6-4}$ or -$NR^{6-2}C(O)R^{6-4}$, then R^{6-4} represents C_6 or C_{10} aryl or a 4-9-membered saturated or unsaturated heterocyclic residue containing up to 2 heteroatoms selected from the group oxygen, nitrogen or sulfur,

wherein the ring formed by R^{6-3} and R^{6-4} can optionally be substituted by 1 to 2 substituents selected from the group C_1-C_4 alkyl, phenyl, C_3-C_7 cycloalkyl, C_1-C_4 alkyloxy, halogen, nitro, cyano,

or

R^2 and R^3 or R^3 and R^4 or R^4 and R^5 together form a 4-7-membered saturated or unsaturated ring containing up to 2 heteroatoms selected from the group oxygen, nitrogen or sulfur, which can optionally be substituted by 1 to 2 substituents selected from the group C_1-C_4 alkyl, phenyl, benzyl, C_3-C_7 cycloalkyl, C_1-C_4 alkyloxy, halogen, nitro, cyano, oxo and which can be fused with a 3-7 membered homocyclic or heterocyclic, saturated, unsaturated or aromatic ring,

A represents -C(O)-, -C(O)-C(O)-, -SO-, $-SO_2$-, -PO-, $-PO_2$-, 2-pyrimidyl, 4-pyrimidyl, 2-pyridyl, 2-imidazolyl, 4-imidazolyl, 2-benzimidazolyl or ~~a~~ ring selected from the following group:



wherein the abovementioned ring systems can optionally be substituted by C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, nitro, amino, cyano,

X represents -$CR^{X-1}R^{X-2}$-,

wherein R^{X-1} and R^{X-2} can be independently selected from the group hydrogen, C_1-C_4 alkyl, C_2 - C_4 alkenyl, C_2-C_4 alkynyl,

or

together with R^6 form a 4-7-membered ring, which can contain up to 2 heteroatoms independently selected from the group oxygen, nitrogen or sulfur and containing up to 2 double bonds, which can optionally be substituted by 1 to 2 substituents selected from the group C_1-C_4 alkyl, phenyl, benzyl, C_3-C_7 cycloalkyl, C_1-C_4 alkyloxy, halogen, nitro, cyano, oxo,

Y represents bond, -C(O)-, -S(O)-, $-SO_2-$, -O-, -S-, $-CR^{Y-1}R^{Y-2}-$, or $-NR^{Y-3}$,

wherein R^{Y-1}, R^{Y-2}, R^{Y-3} can be independently selected from the group bond, hydrogen, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl,

and can optionally be substituted by 1 to 2 substituents independently selected from the group C_1-C_4 alkyl, phenyl, benzyl, C_3-C_7 cycloalkyl, C_1-C_4 alkyloxy, halogen, nitro, cyano, oxo,

D represents N or CR^{D-1},

wherein R^{D-1} can be independently selected from the group bond, hydrogen, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl,

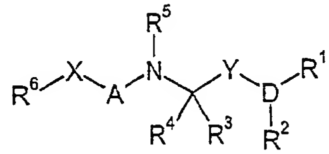
and R^{D-1} can optionally be substituted by 1 to 2 substituents independently selected from the group C_1-C_4 alkyl, phenyl, benzyl, C_3-C_7 cycloalkyl, C_1-C_4 alkyloxy, halogen, nitro, cyano, oxo,

with the proviso that, where D represents –N-, Y does not represent –O- or -S-,

and the compound is not one of the following: 3-[[[(phenylacetyl)amino]acetyl]amino]-benzoic acid; N-(4-aminophenylacetylglycyl)-4-aminophenylacetic acid; N^1-[4-(ethoxycarbonyl)phenyl]-N^2-(phenylacetyl)-α-glutamine; N^2-benzoyl-N^1-[4-(ethoxycarbonyl)phenyl]-α-glutamine; (S)-4-[[4-carboxy-1-oxo-2-[(phenylacetyl)amino]butyl]amino]-benzeneacetic acid; N-[2-[[4-aminosulfonyl)phenyl]amino]-2-oxoethyl]-N-ethylbenzeneacetamide; N-(2-phenylacetylamino-acetylamino)-benzoic acid ethyl ester,

and pharmaceutically acceptable salts thereof.

2. Compounds of the general formula (I) according to claim 1,



(I)

wherein

R^1 represents a 4- to 9-membered saturated, unsaturated or aromatic cyclic residue,

which can contain 0 to 3 heteroatoms selected independently from the group N, S and O,

wherein the cyclic residue R^1 can be annulated with a 4- to 8-membered saturated, unsaturated or aromatic cyclic residue, which can contain 0 to 2 heteroatoms selected independently from the group N, S and O,

and wherein the cyclic residue R^1 and/or a ring annulated to the cyclic residue R^1 is substituted by 1 to 2 substituents $-R^{1-1}-R^{1-2}-R^{1-3}-Z$, wherein

R^{1-1} represents a bond, -O-, -S-, NR^{1-4}, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_6 or C_{10} aryl, C_3-C_7 cycloalkyl or a 4-9-membered saturated or unsaturated heterocyclic residue containing up to 3 heteroatoms selected from the group oxygen, nitrogen or sulfur,

wherein R^{1-1} can optionally be substituted by 1 to 2 substituents selected from the group R^{1-5},

wherein R^{1-5} represents hydrogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_6 or C_{10} aryl, C_3-C_7 cycloalkyl or a 4-9-membered saturated or unsaturated heterocyclic residue containing up to 3 heteroatoms selected from the group oxygen, nitrogen or sulfur,

wherein R^{1-5} can optionally be substituted by 1 to 3 substituents selected from the group C_1-C_4 alkyl, C_1-C_4 alkyloxy, phenyl, C_3-C_6 cycloalkyl, halogen, nitro, cyano, oxo,

R^{1-2} represents a bond, -O-, -S-, NR^{1-4}, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl,

wherein R^{1-2} can optionally be substituted by C_1-C_{10} alkyl, C_2-C_{10} alkenyl, $C_2 - C_{10}$ alkynyl or R^{1-6},

wherein R^{1-6} represents hydrogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_6 or C_{10} aryl, C_3-C_7 cycloalkyl or a 4-9-membered saturated or unsaturated heterocyclic residue containing up to 3 heteroatoms selected from the group oxygen, nitrogen or sulfur,

wherein R^{1-6} can optionally be substituted by 1 to 3 substituents selected from the group C_1-C_4 alkyl, C_1-C_4 alkyloxy, phenyl, C_3-C_6 cycloalkyl, halogen, nitro, cyano, oxo,

R^{1-4} can optionally be hydrogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl or C_2-C_{10} alkynyl,

R^{1-3} represents a bond, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl,

wherein R^{1-3} can optionally be substituted by C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl or R^{1-7} ,

wherein R^{1-7} represents hydrogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_6 or C_{10} aryl, C_3-C_7 cycloalkyl or a 4-9-membered saturated or unsaturated heterocyclic residue containing up to 3 heteroatoms selected from the group oxygen, nitrogen or sulfur,

wherein R^{1-7} can optionally be substituted by 1 to 3 substituents selected from the group C_1-C_4 alkyl, C_1-C_4 alkyloxy, phenyl, C_3-C_6 cycloalkyl, halogen, nitro, cyano, oxo,

with the proviso that, where R^{1-3} is a bond, R^{1-2} is not a heteroatom,

and with the proviso that R^{1-1} and R^{1-2} are not both heteroatom at the same time,

Z represents $-C(O)OR^{Z-1}$, $-C(O)NR^{Z-2}R^{Z-3}$, $-SO_2NR^{Z-2}R^{Z-3}$, $-SO(OR^{Z-1})$, $-SO_2(OR^{Z-1})$, $-P(O)R^{Z-1}(OR^{Z-3})$, $-PO(OR^{Z-1})(OR^{Z-3})$ or 5-tetrazolyl,

wherein R^{Z-2} is hydrogen, C_1-C_4 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6 or C_{10} aryl, $-C(O)R^{Z-4}$ or $-SO_2R^{Z-4}$,

wherein R^{Z-4} is C_1-C_4 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6 or C_{10} aryl,

wherein R^{Z-4} can optionally be substituted by 1 to 3 substituents selected from the group halogen, nitro, cyano, oxo,

R^{Z-1} and R^{Z-3} are identical or different and represent hydrogen, C_1-C_4 alkyl, C_2 -C_6 alkenyl, C_2 -C_6 alkynyl, C_3 -C_6 cycloalkyl, C_6 or C_{10} aryl or benzyl,

wherein R^{Z-1} and R^{Z-3} can optionally be substituted by 1 to 3 substituents selected from the group C_1-C_4 alkyl, C_1-C_4 alkyloxy, halogen, nitro, cyano,

the cyclic residue R^1 and/or a ring annulated to the cyclic residue formed by R^1 can optionally be substituted by 0 to 2 substituents R^{1-8}, halogen, nitro, amino, cyano and oxo,

wherein

R^{1-8} can independently be selected from the group of C_1-C_4 alkyl, C_1-C_4 alkyloxy, phenyl, phenoxy, phenylamino, C_3-C_6 cycloalkyl, and

R^2 represents hydrogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_6 or C_{10} aryl, C_3-C_7 cycloalkyl or a 4-9-membered saturated or unsaturated heterocyclic residue containing up to 2 heteroatoms selected from the group oxygen, nitrogen or sulfur,

which can optionally be substituted by 1 to 3 radicals R^{2-1},

wherein R^{2-1} represents C_{1-4} alkyl, trifluormethyl, trifluormethoxy, $-OR^{2-2}$, $-SR^{2-2}$, $NR^{2-3}R^{2-4}$, $-C(O)R^{2-2}$, $S(O)R^{2-2}$, $-SO_2R^{2-2}$, $-CO_2R^{2-2}$, $-OC(O)R^{2-2}$, $-C(O)NR^{2-3}R^{2-4}$, $-NR^{2-2}C(O)R^{2-3}$, $-SO_2NR^{2-3}R^{2-4}$, $NR^{2-2}SO_2R^{2-3}$, $-NR^{2-2}C(O)NR^{2-3}R^{2-4}$, $-NR^{2-2}C(O)OR^{2-3}$, $-OC(O)NR^{2-3}R^{2-4}$, halogen, cyano, nitro or oxo,

wherein R^{2-2} represents hydrogen, C_1-C_4 alkyl, $C_3 - C_6$ cycloalkyl, C_6 or C_{10} aryl

which can optionally be substituted by 1 substituent selected from the group C_1-C_4 alkyl, C_1-C_4 alkyloxy, phenyl, C_3-C_6 cycloalkyl, halogen, nitro, cyano,

and wherein R^{2-3} and R^{2-4} are identical or different and represent hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_6 or C_{10} aryl,

or

R^{2-3} and R^{2-4} together form a 4-7-membered ring, which includes the nitrogen atom to which R^{2-3} and R^{2-4} are bonded and which contains up to 2 additional heteroatoms selected from the group oxygen, nitrogen or sulfur and which contains up to 2 double bonds,

and if R^2 is alkyl, R^2 together with the cyclic residue R^1 and D can form a ring,

R^3 represents hydrogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_6 or C_{10} aryl, C_3-C_7 cycloalkyl or a 4-9-membered saturated or unsaturated heterocyclic residue containing up to 2 heteroatoms selected from the group oxygen, nitrogen or sulfur,

wherein R^3 can optionally be substituted by 1 to 3 radicals R^{3-1},

and wherein R^3 can furthermore be single-foldedly substituted by C_3-C_7 cycloalkyl, C_6 or C_{10} aryl, C_4-C_9 heteroaryl or a heterocyclic residue containing up to 2 heteroatoms selected from the group oxygen, nitrogen or sulfur,

which can be annulated with a phenyl ring,

and which can optionally be substituted by 1 to 3 radicals R^{3-1},

wherein R^{3-1} represents C_1-C_4 alkyl, trifluormethyl, trifluormethoxy, $-OR^{3-2}$, $-SR^{3-2}$, $NR^{3-3}R^{3-4}$, $-C(O)R^{3-2}$, $S(O)R^{3-2}$, $-SO_2R^{3-2}$, $-OC(O)R^{3-2}$, $-C(O)NR^{3-3}R^{3-4}$, $-NR^{3-2}C(O)R^{3-3}$, $-SO_2NR^{3-3}R^{3-4}$, $NR^{3-2}SO_2R^{3-3}$, $-NR^{3-2}C(O)NR^{3-3}R^{3-4}$, $-NR^{3-2}C(O)OR^{3-3}$, $-OC(O)NR^{3-3}R^{3-4}$, $-CO_2R^{3-5}$, halogen, cyano, nitro or oxo,

wherein R^{3-2} represents hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_6 or C_{10} aryl

which can optionally be substituted by 1 substituent selected from the group C_1-C_4 alkyl, C_1-C_4 alkyloxy, phenyl, C_3-C_6 cycloalkyl, halogen, nitro, cyano,

and wherein R^{3-3} and R^{3-4} are identical or different and represent hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_6 or C_{10} aryl, benzyl or 9-fluorenylmethyl,

or

R^{3-3} and R^{3-4} together form a 4-7-membered ring, which includes the nitrogen atom to which R^{3-3} and R^{3-4} are bonded and which contains up to 2 additional heteroatoms selected from the group oxygen, nitrogen or sulfur and which contains up to 2 double bonds,

and wherein R^{3-5} represents C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_6 or C_{10} aryl

R^4 represents hydrogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_6 or C_{10} aryl, C_3-C_7 cycloalkyl or a 4-9-membered saturated or unsaturated heterocyclic residue containing up to 2 heteroatoms selected from the group oxygen, nitrogen or sulfur,

which can optionally be substituted by 1 to 3 radicals R^{4-1},

and which can furthermore be single-foldedly substituted by C_3-C_7 cycloalkyl, C_6 or C_{10} aryl, C_4-C_9 heteroaryl or a heterocyclic residue containing up to 2 heteroatoms selected from the group oxygen, nitrogen or sulfur,

which can optionally be substituted by 1 to 3 radicals R^{4-1},

wherein R^{4-1} represents $C_1 - C_4$ alkyl, trifluormethyl, trifluormethoxy, $-OR^{4-2}$, $-SR^{4-2}$, $NR^{4-3}R^{4-4}$, $-C(O)R^{4-2}$, $S(O)R^{4-2}$, $-SO_2R^{4-2}$, $-OC(O)R^{4-2}$, $-C(O)NR^{4-3}R^{4-4}$, $-NR^{4-2}C(O)R^{4-3}$, $-SO_2NR^{4-3}R^{4-4}$, $NR^{4-2}SO_2R^{4-3}$, $-NR^{4-2}C(O)NR^{4-3}R^{4-4}$, $-NR^{4-2}C(O)OR^{4-3}$, $-OC(O)NR^{4-3}R^{4-4}$, $-CO_2R^{4-5}$, halogen, cyano, nitro or oxo,

wherein R^{4-2} represents hydrogen, $C_1 - C_4$ alkyl, $C_3 - C_6$ cycloalkyl, C_6 or C_{10} aryl

which can optionally be substituted by 1 substituent selected from the group C_1-C_4 alkyl, C_1-C_4 alkyloxy, phenyl, C_3-C_6 cycloalkyl, halogen, nitro, cyano,

and wherein R^{4-3} and R^{4-4} are identical or different and represent hydrogen, C_{1-4} alkyl, C_3-C_6 cycloalkyl, C_6 or C_{10} aryl,

or

R^{4-3} and R^{4-4} together form a 4-7-membered ring, which includes the nitrogen atom to which R^{4-3} and R^{4-4} are bonded and which contains up to 2 additional heteroatoms selected from the group oxygen, nitrogen or sulfur and which contains up to 2 double bonds,

and wherein R^{4-5} represents $C_1 - C_4$ alkyl, $C_3 - C_6$ cycloalkyl, C_6 or C_{10} aryl

R^5 represents hydrogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_6 or C_{10} aryl, C_3-C_7 cycloalkyl or a 4-9-membered saturated or unsaturated heterocyclic residue containing up to 2 heteroatoms selected from the group oxygen, nitrogen or sulfur,

which can optionally be substituted by 1 to 3 radicals R^{5-1},

and which can furthermore be single-foldedly substituted by C_3-C_7 cycloalkyl, C_6 or C_{10} aryl, C_4-C_9 heteroaryl or a heterocyclic residue containing up to 2 heteroatoms selected from the group oxygen, nitrogen or sulfur,

which can optionally be substituted by 1 to 3 radicals R^{5-1},

wherein R^{5-1} represents C_1-C_4 alkyl, trifluormethyl, trifluormethoxy, $-OR^{5-2}$, $-SR^{5-2}$, $NR^{5-3}R^{5-4}$, $-C(O)R^{5-2}$, $S(O)R^{5-2}$, $-SO_2R^{5-2}$, $-CO_2R^{5-2}$, $-OC(O)R^{5-2}$, $-C(O)NR^{5-3}R^{5-4}$, $-NR^{5-2}C(O)R^{5-3}$, $-SO_2NR^{5-3}R^{5-4}$, $NR^{5-2}SO_2R^{5-3}$, $-NR^{5-2}C(O)NR^{5-3}R^{5-4}$, $-NR^{5-2}C(O)OR^{5-3}$, $-OC(O)NR^{5-3}R^{5-4}$, ~~,~~ halogen, cyano, nitro or oxo,

wherein R^{5-2} represents hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_6 or C_{10} aryl

which can optionally be substituted by 1 substituent selected from the group C_1-C_4 alkyl, C_1-C_4 alkyloxy, phenyl, C_3-C_6 cycloalkyl, halogen, nitro, cyano,

and wherein R^{5-3} and R^{5-4} are identical or different and represent hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_6 or C_{10} aryl,

or

R^{5-3} and R^{5-4} together form a 4-7-membered ring, which includes the nitrogen atom to which R^{5-3} and R^{5-4} are bonded and which contains up to 2 additional heteroatoms selected from the group oxygen, nitrogen or sulfur and which contains up to 2 double bonds,

R^6 represents phenyl or a 5- to 6-membered aromatic heterocyclic residue containing up to 3 heteroatoms independently selected from the group oxygen, nitrogen or sulfur,

which can optionally be annulated with a 5- to 8-membered saturated or unsaturated cyclic residue containing up to 2 heteroatoms independently selected from the group oxygen, nitrogen or sulfur,

and which can optionally be independently substituted by 1 to 3 radicals R^{6-1} and which can furthermore be single-foldedly substituted by C_3-C_7 cycloalkyl, C_6 or C_{10} aryl, C_4-C_9 heteroaryl or a heterocyclic residue containing up to 2 heteroatoms selected from the group oxygen, nitrogen or sulfur,

wherein the latter cyclic substituents can themselves optionally be substituted by 1 to 3 radicals R^{6-1},

wherein R^{6-1} represents C_1-C_4 alkyl, trifluormethyl, trifluormethoxy, $-OR^{6-4}$, $-SR^{6-2}$, $NR^{6-3}R^{6-4}$, $-C(O)R^{6-2}$, $S(O)R^{6-2}$, $-SO_2R^{6-2}$, $-CO_2R^{6-2}$, $-OC(O)R^{6-2}$, $-C(O)NR^{6-3}R^{6-4}$, $-NR^{6-2}C(O)R^{6-2}$, $-SO_2NR^{6-3}R^{6-4}$, $-NR^{6-2}SO_2R^{6-2}$, $-NR^{6-2}C(O)NR^{6-3}R^{6-4}$, $-NR^{6-2}C(O)OR^{6-4}$, $-OC(O)NR^{6-3}R^{6-4}$, halogen, cyano, nitro or oxo,

wherein R^{6-2} represents hydrogen, C_1-C_4 alkyl, $C_3 - C_6$ cycloalkyl, C_6 or C_{10} aryl

which can optionally be substituted by 1 to 3 substituents selected from the group C_1-C_4 alkyl, C_1-C_4 alkyloxy, phenyl, C_3-C_6 cycloalkyl, halogen, nitro, cyano,

and wherein R^{6-3} and R^{6-4} are identical or different and represent hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_6 or C_{10} aryl or a 4-9-membered saturated or unsaturated heterocyclic residue containing up to 2 heteroatoms selected from the group oxygen, nitrogen or sulfur,

which can optionally be substituted by 1 to 2 substituents selected from the group C_1-C_4 alkyl, phenyl, C_3-C_7 cycloalkyl, C_1-C_4 alkyloxy, halogen, nitro, cyano,

or

R^{6-3} and R^{6-4} together form a 4-7-membered ring, which includes the nitrogen atom to which R^{6-3} and R^{6-4} are bonded and which contains up to 2 additional heteroatoms selected from the group oxygen, nitrogen or sulfur and which contains up to 2 double bonds, which can optionally be substituted by 1 to 2 substituents selected from the group C_1-C_4 alkyl, phenyl, benzyl, C_3-C_7 cycloalkyl, C_1-C_4 alkyloxy, halogen, nitro, cyano, oxo,

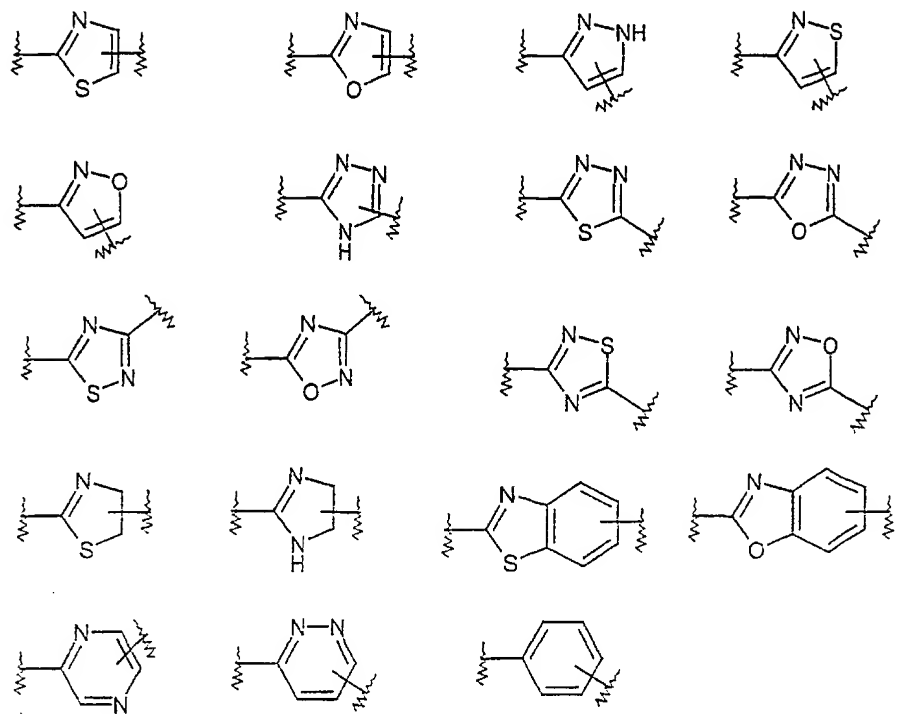
and in case that R^1 represents a 3-amino benzoic acid derivative and R^{6-1} represents $-OR^{6-4}$, $-C(O)NR^{6-3}R^{6-4}$ or $-NR^{6-2}C(O)R^{6-4}$, then R^{6-4} represents C_6 or C_{10} aryl or a 4-9-membered saturated or unsaturated heterocyclic residue containing up to 2 heteroatoms selected from the group oxygen, nitrogen or sulfur,

wherein the ring formed by R^{6-3} and R^{6-4} can optionally be substituted by 1 to 2 substituents selected from the group C_1-C_4 alkyl, phenyl, C_3-C_7 cycloalkyl, C_1-C_4 alkyloxy, halogen, nitro, cyano,

or

R^3 and R^4 or R^4 and R^5 together form a 4-7-membered saturated or unsaturated ring containing up to 2 heteroatoms selected from the group oxygen, nitrogen or sulfur, which can optionally be substituted by 1 to 2 substituents selected from the group C_1-C_4 alkyl, phenyl, benzyl, C_3-C_7 cycloalkyl, C_1-C_4 alkyloxy, halogen, nitro, cyano, oxo and which can be fused with a 3-7 membered homocyclic or heterocyclic, saturated, unsaturated or aromatic ring,

A represents -C(O)-, -C(O)-C(O)-, -SO-, $-SO_2-$, -PO-, $-PO_2-$, 2-pyrimidyl, 4-pyrimidyl, 2-pyridyl, 2-imidazolyl, 4-imidazolyl, 2-benzimidazolyl or a ring selected from the following group:



wherein the abovementioned ring systems can optionally be substituted by C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, nitro, amino, cyano,

X represents -$CR^{X-1}R^{X-2}$-,

wherein R^{X-1} and R^{X-2} can be independently selected from the group hydrogen, C_1-C_4 alkyl, C_2 - C_4 alkenyl, C_2-C_4 alkynyl,

or

together with R^6 form a 4-7-membered ring, which can contain up to 2 heteroatoms independently selected from the group oxygen, nitrogen or sulfur and containing up to 2 double bonds, which can optionally be substituted by 1 to 2 substituents selected from the group C_1-C_4 alkyl, phenyl, benzyl, C_3-C_7 cycloalkyl, C_1-C_4 alkyloxy, halogen, nitro, cyano, oxo,

Y represents bond, -C(O)-, -S(O)-, $-SO_2-$, -O-, -S-, $-CR^{Y-1}R^{Y-2}-$, or $-NR^{Y-3}$,

wherein R^{Y-1}, R^{Y-2}, R^{Y-3} can be independently selected from the group bond, hydrogen, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl,

and can optionally be substituted by 1 to 2 substituents independently selected from the group C_1-C_4 alkyl, phenyl, benzyl, C_3-C_7 cycloalkyl, C_1-C_4 alkyloxy, halogen, nitro, cyano, oxo,

D represents N or CR^{D-1},

wherein R^{D-1} can be independently selected from the group bond, hydrogen, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl,

and R^{D-1} can optionally be substituted by 1 to 2 substituents independently selected from the group C_1-C_4 alkyl, phenyl, benzyl, C_3-C_7 cycloalkyl, C_1-C_4 alkyloxy, halogen, nitro, cyano, oxo,

with the proviso that, where D represents –N-, Y does not represent –O- or -S-,

and the compound is not one of the following: 3-[[[(phenylacetyl)amino]acetyl]amino]-benzoic acid; N-(4-aminophenylacetylglycyl)-4-aminophenylacetic acid; N^1-[4-(ethoxycarbonyl)phenyl]-N^2-(phenylacetyl)-α-glutamine; N^2-benzoyl-N^1-[4-(ethoxycarbonyl)phenyl]-α-glutamine; (S)-4-[[4-carboxy-1-oxo-2-[(phenylacetyl)amino]butyl]amino]-benzeneacetic acid; N-[2-[[4-aminosulfonyl)phenyl]amino]-2-oxoethyl]-N-ethylbenzeneacetamide; N-(2-phenylacetylamino-acetylamino)-benzoic acid ethyl ester,

and pharmaceutically acceptable salts thereof.

3. Compounds according to claim 1 or 2,

wherein

R^1 represents a 4- to 6-membered saturated, unsaturated or aromatic cyclic residue,

which can contain 0 to 3 heteroatoms selected independently from the group N, S and O,

wherein the cyclic residue R^1 can be annulated with a 5- to 6-membered saturated, unsaturated or aromatic cyclic residue, which can contain 0 to 2 heteroatoms selected independently from the group N, S and O,

and wherein the cyclic residue R^1 and/or a ring annulated to the cyclic residue R^1 is substituted by 1 to 2 substituents $–R^{1-1}–R^{1-2}–R^{1-3}–Z$, wherein

R^{1-1} represents a bond, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or C_6 aryl,

wherein R^{1-1} can optionally be substituted by 1 substituent selected from the group R^{1-5}, wherein R^{1-5} represents hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl or C_6 aryl,

R^{1-2} represents a bond, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl

R^{1-3} represents a bond, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl

Z represents $-C(O)OR^{Z-1}$, $-C(O)NR^{Z-2}R^{Z-3}$ or 5-tetrazolyl,

wherein R^{Z-1}, R^{Z-2} and R^{Z-3} are identical or different and represent hydrogen, C_1-C_4 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or benzyl,

the cyclic residue R^1 and/or a ring annulated to the cyclic residue formed by R^1 can optionally be substituted by 0 to 2 substituents R^{1-8}, halogen, nitro, amino, cyano and oxo,

wherein

R^{1-8} can independently be selected from the group of C_1-C_4 alkyl, C_1-C_4 alkyloxy, phenyl, phenoxy, phenylamino,

R^2 represents hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_6 aryl, C_5-C_6 cycloalkyl,

and if R^2 is alkyl, R^2 together with the cyclic residue R^1 and D can form a 5- to 6-membered ring,

R^3 represents hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_6 aryl, C_5-C_6 cycloalkyl or a 5-6-membered saturated or unsaturated heterocyclic residue containing up to 2 heteroatoms selected from the group oxygen, nitrogen or sulfur,

which can optionally be substituted by 1 radical R^{3-1},

and wherein R^3 can furthermore be single-foldedly substituted by C_3-C_7 cycloalkyl, C_6 aryl, C_4-C_9 heteroaryl or a heterocyclic residue containing up to 2 heteroatoms selected from the group oxygen, nitrogen or sulfur,
which can be annulated with a phenyl ring,

wherein R^{3-1} represents trifluormethyl, trifluormethoxy, $-OR^{3-2}$, $-SR^{3-2}$, $NR^{3-3}R^{3-4}$, $-NR^{3-2}C(O)OR^{3-3}$, $-CO_2R^{3-5}$, halogen, cyano, nitro or oxo,

wherein R^{3-2} represents hydrogen or C_1-C_4 alkyl,

and wherein R^{3-3} and R^{3-4} are identical or different and represent hydrogen, C_1-C_4 alkyl or benzyl or 9-fluorenylmethyl,

and wherein R^{3-5} represents C_1-C_4 alkyl,

R^4 represents hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 or C_6 aryl,

R^5 represents hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or C_6 aryl,

which can optionally be substituted by 1 radical R^{5-1},

wherein R^{5-1} represents trifluormethyl, trifluormethoxy, $-OR^{5-2}$, $-SR^{5-2}$, $NR^{5-3}R^{5-4}$, halogen, cyano, nitro or oxo,

wherein R^{5-2}, R^{5-3} and R^{5-4} are identical or different and represent hydrogen or C_1-C_4 alkyl,

R^6 represents phenyl or a 5- to 6-membered aromatic heterocyclic residue containing up to 3 heteroatoms independently selected from the group oxygen, nitrogen or sulfur,

and which can optionally be independently substituted by 1 to 3 radicals R^{6-1}

wherein R^{6-1} represents $-NR^{6-2}C(O)NR^{6-3}R^{6-4}$,

wherein R^{6-2} and R^{6-3} are identical or different and represent hydrogen or C_1-C_4 alkyl,

and wherein R^{6-4} represents C_6 aryl,

which can optionally be substituted by 1-2 substituents selected from the group C_1-C_4 alkyl, C_1-C_4 alkyloxy, halogen, nitro, cyano,

or R^3 and R^4 or R^4 and R^5 together form a 5-6-membered saturated or unsaturated ring containing up to 2 nitrogen atoms,

A represents -C(O)-, -SO-, $-SO_2-$,

X represents $-CR^{X-1}R^{X-2}$,

wherein R^{X-1} and R^{X-2} can be independently selected from the group hydrogen, C_1-C_4 alkyl,

Y represents -C(O)-,

D represents -N-,

and pharmaceutically acceptable salts thereof.

4. Compounds according to claim 1, 2 or 3,

wherein

R^1 represents a 5- to 6-membered saturated, unsaturated or aromatic cyclic residue,

which can contain 0 to 3 heteroatoms selected independently from the group N and S,

wherein the cyclic residue R^1 can be annulated with a 5-membered unsaturated or aromatic cyclic residue, which contains 1 nitrogen atom,

and wherein the cyclic residue R^1 and/or a ring annulated to the cyclic residue R^1 is substituted by 1 to 2 substituents $-R^{1-1}-R^{1-2}-R^{1-3}-Z$, wherein

R^{1-1} represents a bond or C_1 alkyl,

wherein R^{1-1} can optionally be substituted by cyclopentyl,

R^{1-2} represents a bond,

R^{1-3} represents a bond,

Z represents $-C(O)OR^{Z-1}$ or 5-tetrazolyl,

R^{Z-1} represents hydrogen, C_1-C_2 alkyl or benzyl,

the cyclic residue R^1 can optionally be substituted by 0 to 2 substituents R^{1-8}, halogen and nitro,

wherein

R^{1-8} can independently be selected from the group of C_1-C_4 alkyloxy, phenoxy and phenylamino,

R^2 represents hydrogen or C_1-C_3 alkyl,

or

and if R^2 is alkyl, R^2 together with the cyclic residue R^1 and D can form a piperidine ring,

R^3 represents hydrogen or C_1-C_4 alkyl,

which can optionally be substituted by 1 radical R^{3-1},

wherein R^{3-1} represents $NR^{3-3}R^{3-4}$ or $-NR^{3-2}C(O)OR^{3-3}$,

wherein R^{3-2} and R^{3-4} represent hydrogen,

R^{3-3} represents hydrogen, benzyl or 9-fluorenylmethyl,

R^4 represents hydrogen,

R^5 represents hydrogen or C_3 alkyl,

which can optionally be substituted by 1 radical R^{5-1},

wherein R^{5-1} represents $-OR^{5-2}$,

wherein R^{5-2} represents C_1 alkyl,

R^6 represents phenyl,

and which is substituted by 1 radical R^{6-1}

wherein R^{6-1} represents $-NR^{6-2}C(O)NR^{6-3}R^{6-4}$,

wherein R^{6-2} represents hydrogen,

and wherein R^{6-3} represents hydrogen

and R^{6-4} represents C_6 aryl,

which is substituted by 1 substituent C_1 alkyl,

A represents -C(O)-,

X represents $-CR^{X-1}R^{X-2}-$,

wherein R^{X-1} and R^{X-2} represent hydrogen,

Y represents -C(O)-,

D represents N,

and pharmaceutically acceptable salts thereof.

5. Compounds according to claim 1, 2 or 3,

wherein

R^1 represents phenyl,

and wherein the phenyl is substituted by 1 to 2 substituents $-R^{1-1}-R^{1-2}-R^{1-3}-Z$,

wherein

R^{1-1} represents a bond or C_1 alkyl,

R^{1-2} represents a bond,

R^{1-3} represents a bond,

Z represents -C(O)OR^{Z-1}

R^{Z-1} represents hydrogen, C_1-C_2 alkyl or benzyl,

R^2 represents hydrogen,

R^3 represents hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_6 aryl, C_5-C_6 cycloalkyl or a 5-6-membered saturated or unsaturated heterocyclic residue containing up to 2 heteroatoms selected from the group oxygen, nitrogen or sulfur,

which can optionally be substituted by 1 radical R^{3-1},

and wherein R^3 can furthermore be single-foldedly substituted by C_3-C_7 cycloalkyl, C_6 aryl, C_4-C_9 heteroaryl or a heterocyclic residue containing up to 2 heteroatoms selected from the group oxygen, nitrogen or sulfur,

which can be annulated with a phenyl ring,

wherein R^{3-1} represents trifluormethyl, trifluormethoxy, -OR^{3-2}, -SR^{3-2}, -N$R^{3-3}R^{3-4}$, -NR^{3-2}C(O)OR^{3-3}, -CO_2R^{3-5}, halogen, cyano, nitro or oxo,

wherein R^{3-2} represents hydrogen or C_1-C_4 alkyl,

and wherein R^{3-3} and R^{3-4} are identical or different and represent hydrogen, C_1-C_4 alkyl or benzyl or 9-fluorenylmethyl,

and wherein R^{3-5} represents C_1-C_4 alkyl,

R^4 represents hydrogen,

R^5 represents hydrogen ,

R^6 represents phenyl,

and which is substituted by 1 radical R^{6-1}

wherein R^{6-1} represents $-NR^{6-2}C(O)NR^{6-3}R^{6-4}$,

wherein R^{6-2} represents hydrogen,

and wherein R^{6-3} represents hydrogen

and R^{6-4} represents C_6 aryl,

which is substituted by 1 substituent C_1 alkyl,

or R^3 and R^4 or R^4 and R^5 together form a 5-6-membered saturated or a unsaturated ring containing up to 2 nitrogen atoms,

A represents -C(O)-,

X represents $-CR^{X-1}R^{X-2}-$,

wherein R^{X-1} and R^{X-2} represent hydrogen,

Y represents -C(O)-,

D represents N,

and pharmaceutically acceptable salts thereof.

6. Compounds according to any one of claims 1 to 5,

wherein

R^1 represents phenyl,

which is 1,4-substituted by a substituent $-R^{1-1}-R^{1-2}-R^{1-3}-Z$,

wherein

R^{1-1}, R^{1-2} and R^{1-3} represent bonds.

7. Compounds according to any one of claims 1 to 5,

wherein

R^1 represents phenyl,

which is 1,3-substituted by a substituent $-R^{1-1}-R^{1-2}-R^{1-3}-Z$,

wherein

R^{1-1} represents $-CH_2-$,

R^{1-2} and R^{1-3} represent bonds.

8. Compounds according to any one of claims 1 to 5,

wherein

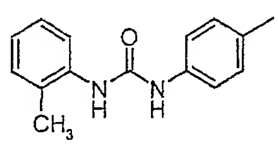
R^1 represents a 5-membered heterocycle.

9. Compounds according to any one of claims 1 to 5,

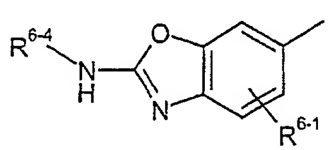
wherein

R^1 represents a cyclohexyl ring.

10. Compounds according to any one of claims 1 to 5, wherein R^6 represents



11. Compounds according to any one of claims 1 to 5, wherein R^6 represents



12. Compounds according to claim 1, wherein

R^5 represents hydrogen, C_1-C_4 alkyl,

which can optionally be substituted by 1 radicals R^{5-1},

and which can furthermore be single-foldedly substituted by C_6 or C_{10} aryl, C_4-C_9 heteroaryl or a saturated or unsaturated heterocyclic residue containing up to 2 heteroatoms selected from the group oxygen, nitrogen or sulfur,

which can optionally be substituted by 1 to 3 radicals R^{5-1},

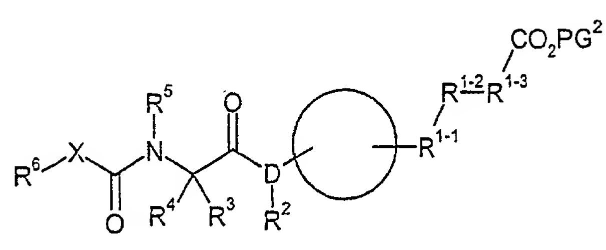
wherein R^{5-1} is independently selected from the group C_1-C_4 alkyl, phenyl, trifluormethyl, trifluormethoxy, -OR^{5-2}, $NR^{5-3}R^{5-4}$, halogen or oxo,

wherein R^{5-2} represents hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl or C_6 aryl

which can optionally be substituted by 1 substituent selected from the group C_1-C_4 alkyl, C_1-C_4 alkyloxy, phenyl, C_3-C_6 cycloalkyl or halogen,

and wherein R^{5-3} and R^{5-4} are identical or different and represent hydrogen, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_6 aryl.

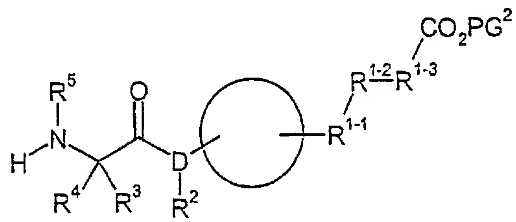
13. A process for preparation of compounds of general formula (VII),



(VII)

according to any one of claims 5 to 9,

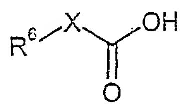
which comprises reaction of carboxylic acids of general formula (V)



(V)

or activated derivatives thereof

with compounds of the general formula (VI)



(VI)

in the presence of a coupling agent and a base in inert solvents.

14. Compounds according to any one of claims 1 to 8, wherein the compound is selected from the following group:

N^2-{[4-({[(2-methylphenyl)amino]carbonyl}amino)phenyl]acetyl}-N^1-[4-(1H-tetraazol-5-yl)phenyl]-L-leucinamide,

2-[(N-{[4-({[(2-methylphenyl)amino]carbonyl}amino)phenyl]acetyl}-L-leucyl)amino]benzoic acid,

3-[(N-{[4-({[(2-methylphenyl)amino]carbonyl}amino)phenyl]acetyl}-L-leucyl)amino]benzoic acid,

4-[(N-{[4-({[(2-methylphenyl)amino]carbonyl}amino)phenyl]acetyl}-L-leucyl)amino]benzoic acid,

{2-[(N-{[4-({[(2-methylphenyl)amino]carbonyl}amino)phenyl]acetyl}-L-leucyl)amino]phenyl}acetic acid,

{3-[(N-{[4-({[(2-methylphenyl)amino]carbonyl}amino)phenyl]acetyl}-L-leucyl)amino]phenyl}acetic acid,

{4-[(N-{[4-({[(2-methylphenyl)amino]carbonyl}amino)phenyl]acetyl}-L-leucyl)amino]phenyl}acetic acid,

3-chloro-4-[(N-{[4-({[(2-methylphenyl)amino]carbonyl}amino)phenyl]acetyl}-L-leucyl)amino]benzoic acid,

3-methoxy-4-[(N-{[4-({[(2-methylphenyl)amino]carbonyl}amino)phenyl]acetyl}-L-leucyl)amino]benzoic acid,

2-chloro-4-[(N-{[4-({[(2-methylphenyl)amino]carbonyl}amino)phenyl]acetyl}-L-leucyl)amino]benzoic acid,

2-anilino-4-[(N-{[4-({[(2-methylphenyl)amino]carbonyl}amino)phenyl]acetyl}-L-leucyl)amino]benzoic acid,

4-[(N-{[4-({[(2-methylphenyl)amino]carbonyl}amino)phenyl]acetyl}-L-leucyl)amino]-2-phenoxybenzoic acid,

2,5-dichloro-4-[(N-{[4-({[(2-methylphenyl)amino]carbonyl}amino)phenyl]acetyl}-L-leucyl)amino]benzoic acid,

3-[(N-{[4-({[(2-methylphenyl)amino]carbonyl}amino)phenyl]acetyl}-L-leucyl)amino]-5-nitrobenzoic acid,

1-(N-{[4-({[(2-methylphenyl)amino]carbonyl}amino)phenyl]acetyl}-L-leucyl)-1,2,3,4-tetrahydro-6-quinolinecarboxylic acid,

4-{[(N-{[4-({[(2-methylphenyl)amino]carbonyl}amino)phenyl]acetyl}-L-leucyl)amino]methyl}benzoic acid,

cyclopentyl{4-[(N-{[4-({[(2-methylphenyl)amino]carbonyl}amino)phenyl]acetyl}-L-leucyl)amino]phenyl}acetic acid,

{2-[(N-{[4-({[(2-methylphenyl)amino]carbonyl}amino)phenyl]acetyl}-L-leucyl)amino]-1,3-thiazol-4-yl}acetic acid,

{5-[(N-{[4-({[(2-methylphenyl)amino]carbonyl}amino)phenyl]acetyl}-L-leucyl)amino]-1,3,4-thiadiazol-2-yl}acetic acid,

{2-[methyl(N-{[4-({[(2-methylphenyl)amino]carbonyl}amino)phenyl]acetyl}-L-leucyl)amino]-1,3-thiazol-4-yl}acetic acid,

5-[(N-{[4-({[(2-methylphenyl)amino]carbonyl}amino)phenyl]acetyl}-L-leucyl)amino]-1H-indole-2-carboxylic acid

N^1-(4-carboxyphenyl)-N^2-{[4-({[(2-methylphenyl)amino]carbonyl}amino)phenyl]acetyl}-L-lysinamide trifluoroacetate,

4-[(N-(3-methoxypropyl)-N-{[4-({[(2-methylphenyl)amino]carbonyl}amino)phenyl]acetyl}glycyl)amino]benzoic acid,

4-[(N-{[4-({[(2-methylphenyl)amino]carbonyl}amino)phenyl]acetyl}-L-leucyl)amino]cyclohexanecarboxylic acid and

(1R,2S)-2-[(N-{[4-({[(2-methylphenyl)amino]carbonyl}amino)phenyl]acetyl}-L-leucyl)amino]cyclohexanecarboxylic acid.

15. The use of a compound according to any one of claims 1 to 5 in the manufacture of a medicament.

16. The use of a compound according to any one of claims 1 to 5 in the manufacture of a medicament for the treatment or the prevention of a condition mediated by integrins.

17. The use of a compound according to any one of claims 1 to 5 in the manufacture of a medicament for the treatment or the prevention of atherosclerosis, asthma, chronic obstructive pulmonary disease (COPD), allergies, diabetes, inflammatory bowel disease, multiple sclerosis, myocardial ischemia, rheumatoid arthritis, transplant rejection and other inflammatory, autoimmune and immune disorders.

18. Pharmaceutical composition, comprising compounds according to any one of claims 1 to 5 and a pharmaceutically acceptable carrier.

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(19) World Intellectual Property Organization
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(10) International Publication Number
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(74) Common Representative: **BAYER AKTIENGESELLSCHAFT**; 51368 Leverkusen (DE).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

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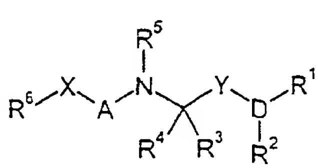
Published:
— *with international search report*

(88) Date of publication of the international search report: 2 May 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/81298 A3

(54) Title: CYCLIC CARBOXYLIC ACIDS AS INTEGRIN ANTAGONISTS



(I)

(57) Abstract: The present invention relates to compounds of general formula (I), processes for their preparation, pharmaceutical compositions containing them as well as their use for the production of pharmaceutical compositions for the treatment of inflammatory diseases.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 01/04043

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C271/22 C07C275/42 C07D257/04 C07D277/44 C07D285/08
A61K31/185 A61K31/17 A61K31/41 A61K31/425 A61K31/433
A61P29/00 C07C237/20 C07D209/42 C07D215/48 C07D285/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 96 22966 A (BIOGEN INC ;ADAMS STEVEN P (US); LIN KO CHUNG (US); LEE WEN CHERNG) 1 August 1996 (1996-08-01) cited in the application claim 1	14
Y	WO 99 33789 A (MORLEY ANDREW DAVID ;RHONE POULENC RORER LTD (GB); ASTLES PETER CH) 8 July 1999 (1999-07-08) cited in the application tables 3-15	14
Y	WO 99 37605 A (NOVARTIS ERFIND VERWALT GMBH ;NOVARTIS AG (CH); VON MATT PETER JOS) 29 July 1999 (1999-07-29) cited in the application claim 11	14

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 January 2002	25/01/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Goetz, G

Form PCT/ISA/210 (second sheet) (July 1992)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-13, 15-18 (all in part)

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claim(s) is impossible. Consequently, the search has been restricted to the compounds of present claim 14 as well as to the use of these compounds

In addition, present claims 1 to 13 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds as claimed in present claim 14 as well to the use of these compounds.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 01/04043

Patent document cited in search report		Publication date	Patent family member(s)			Publication date
WO 9622966	A	01-08-1996	US	6306840	B1	23-10-2001
			AU	718926	B2	04-05-2000
			AU	4911596	A	14-08-1996
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			BR	9606778	A	06-01-1998
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WO 9933789	A	08-07-1999	AU	1771999	A	19-07-1999
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			CN	1294576	T	09-05-2001
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			EP	1049665	A1	08-11-2000
			HU	0100336	A2	30-07-2001
			NO	20003694	A	20-09-2000
			PL	341899	A1	07-05-2001